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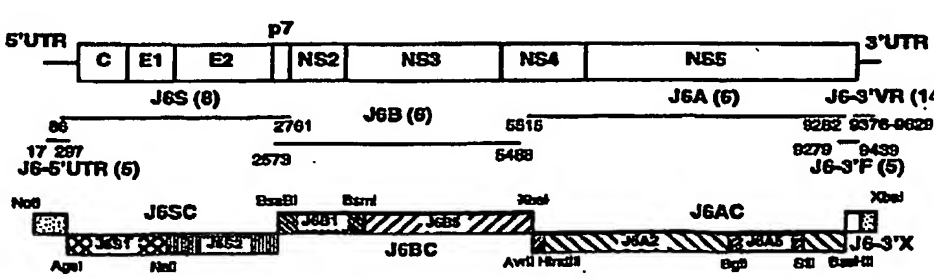
(54) Title: CLONED GENONE OF INFECTIOUS HEPATITIS C VIRUS OF GENOTYPE 2a AND USES THEREOF



(57) Abstract: The present invention discloses nucleic acid sequence which encodes infectious hepatitis C virus of strain HC-J6$_{CH}$, genotype 2a, and the use of the sequence, and polypeptides encoded by all or part of the sequence, in the development of vaccines and diagnostics for HCV and in the development of screening assays for the identification of antiviral agents for HCV.

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Title Of Invention

Cloned Genome Of Infectious Hepatitis C Virus of Genotype 2a And Uses Thereof

Field Of Invention

The present invention relates to molecular approaches to the production of nucleic acid sequence which comprises the genome of infectious hepatitis C virus. In particular, the invention provides a nucleic acid sequence which comprises the genome of an infectious hepatitis C virus of genotype 2a. The invention therefore relates to the use of the nucleic acid sequence and polypeptides encoded by all or part of the sequence in the development of vaccines and diagnostic assays for HCV and in the development of screening assays for the identification of antiviral agents for HCV.

Background Of Invention

Hepatitis C virus (HCV) has a positive-sense single-strand RNA genome and is a member of the genus *Hepacivirus* within the *Flaviviridae* family of viruses (Rice, 1996). As for all positive-stranded RNA viruses, the genome of HCV functions as mRNA from which all viral proteins necessary for propagation are translated.

The viral genome of HCV is approximately 9600 nucleotides (nts) in length and consists of a highly conserved 5' untranslated region (UTR), a single long open reading frame (ORF) of approximately 9,000 nts and a complex 3' UTR. The 5' UTR contains an internal ribosomal entry site (Tsukiyama-Kohara et al., 1992;

Honda et al., 1996). The 3' UTR consists of a short variable region, a polypyrimidine tract of variable length and, at the 3' end, a highly conserved region of approximately 100 nucleotides (Kolykhalov et al., 1996; Tanaka et al., 1995; Tanaka et al., 1996; Yamada et al., 1996). The last 46 nucleotides of this conserved region were predicted to form a stable stem-loop structure thought to be critical for viral replication (Blight and Rice, 1997; Ito and Lai, 1997; Tsuchihara et al., 1997). The ORF encodes a large polypeptide precursor that is cleaved into at least 10 proteins by host and viral proteinases (Rice, 1996). The predicted envelope proteins contain several conserved N-linked glycosylation sites and cysteine residues (Okamoto et al., 1992a). The NS3 gene encodes a serine protease and an RNA helicase and the NS5B gene encodes an RNA-dependent RNA polymerase.

A remarkable characteristic of HCV is its genetic heterogeneity, which is manifested throughout the genome (Bukh *et al.*, 1995). The most heterogeneous regions of the genome are found in the envelope genes, in particular the hypervariable region 1 (HVR1) at the N-terminus of E2 (Hijikata *et al.*, 1991; Weiner *et al.*, 1991). HCV circulates as a quasispecies of closely related genomes in an infected individual. Globally, six major HCV genotypes (genotypes 1-6) and multiple subtypes (a, b, c, etc.) have been identified (Bukh et al., 1993; Simmonds et al., 1993).

The nucleotide and deduced amino acid sequences among isolates within a quasispecies generally differ by < 2%, whereas those between isolates of different genotypes vary by as much as 35%. Genotypes

1, 2 and 3 are found worldwide and constitute more than 90% of the HCV infections in North and South America, Europe, Russia, China, Japan and Australia (Forns and Bukh, 1998). Throughout these regions genotype 1 accounts for the majority of HCV infections but genotypes 2 and 3 each account for 5-15%.

At present, more than 80% of individuals infected with HCV become chronically infected and these chronically infected individuals have a relatively high risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (Hoofnagle, 1997). The only effective therapy for chronic hepatitis C, interferon (IFN), alone or in combination with ribavirin, induces a sustained response in less than 50% of treated patients (Davis et al., 1998; McHutchinson et al., 1998). Consequently, HCV is currently the most common cause of end stage liver failure and the reason for about 30% of liver transplants performed in the U.S. (Hoofnagle, 1997). In addition, a number of recent studies suggested that the severity of liver disease and the outcome of therapy may be genotype-dependent (reviewed in Bukh et al., 1997). In particular, these studies suggested that infection with HCV genotype 1b was associated with more severe liver disease (Brechot, 1997) and a poorer response to IFN therapy (Fried and Hoofnagle, 1995). As a result of the inability to develop a universally effective therapy against HCV infection, it is estimated that there are still more than 25,000 new infections yearly in the U.S. (Alter 1997) Moreover, since there is no vaccine for HCV, HCV remains a serious public health problem.

Despite the intense interest in the development of vaccines and therapies for HCV, progress has been hindered by the absence of a useful cell culture system and the lack of any small animal model for laboratory study. For example, while replication of HCV in several cell lines has been reported, such observations have turned out not to be highly reproducible. In addition, the chimpanzee is the only animal model, other than man, for this disease. Consequently, HCV has been studied only by using clinical materials obtained from patients or experimentally infected chimpanzees, an animal model whose availability is very limited.

However, several researchers have recently reported the construction of infectious cDNA clones of HCV, the identification of which would permit a more effective search for susceptible cell lines and facilitate molecular analysis of the viral genes and their function. For example, Yoo et al., and Dash et al., (1997) (1995) reported that RNA transcripts from cDNA clones of HCV-1 (genotype 1a) and HCV-N (genotype 1b), respectively, resulted in viral replication after transfection into human hepatoma cell lines. Unfortunately, the viability of these clones was not tested <u>in vivo</u> and concerns were raised about the infectivity of these cDNA clones <u>in vitro</u> (Fausto, 1997). In addition, both clones did not contain the terminal 98 conserved nucleotides at the very 3' end of the UTR.

Kolykhalov et al., (1997) and Yanagi et al. (1997, 1998) reported the derivation from HCV strains H77 (genotype 1a) and HC-J4 (genotype 1b) of cDNA clones

of HCV that are infectious for chimpanzees. However, while these infectious clones will aid in studying HCV replication and pathogenesis and will provide an important tool for development of in vitro replication and propagation systems, it is important to have infectious clones of more than one genotype, given the extensive genetic heterogeneity of HCV and the potential impact of such heterogeneity on the development of effective therapies and vaccines for HCV.

In addition, synthetic chimeric viruses can be used to map the functional regions of viruses with different phenotypes. In flaviviruses and pestiviruses, infectious chimeric viruses have been successfully engineered to express different functional units of related viruses (Bray and Lai, 1991; Pletnev *et al.*, 1992, 1998; Vassilev *et al.*, 1997) and in some cases it has been possible to make chimeras between non-related or distantly related viruses. For instance, the IRES element of poliovirus or bovine viral diarrhea virus has been replaced with IRES sequences from HCV (Frolov *et al.*, 1998; Lu and Wimmer, 1996; Zhao *et al.*, 1999). Recently, the construction of an infectious chimera of two closely related HCV subtypes has been reported. The chimera contained the complete ORF of a genotype 1b strain but had the 5' and 3' termini of a genotype 1a strain (Yanagi *et al.*, 1998).

It is important to determine whether chimeras constructed from more divergent HCV strains are infectious because such chimeras could be used to define the functions of viral units and to dissect the immune response.

Summary Of The Invention

The present invention relates to nucleic acid sequence which comprises the genome of infectious hepatitis C virus and in particular, nucleic acid sequence which comprises the genome of infectious hepatitis C virus of genotype 2a. It is therefore an object of the invention to provide nucleic acid sequence which encodes infectious hepatitis C virus. Such nucleic acid sequence is referred to throughout the application as "infectious nucleic acid sequence".

For the purposes of this application, nucleic acid sequence refers to RNA, DNA, cDNA or any variant thereof capable of directing host organism synthesis of a hepatitis C virus polypeptide. It is understood that nucleic acid sequence encompasses nucleic acid sequences, which due to degeneracy, encode the same polypeptide sequence as the nucleic acid sequences described herein.

The invention also relates to the use of the infectious nucleic acid sequences to produce chimeric genomes consisting of portions of the open reading frames of nucleic acid sequences of other genotypes (including, but not limited to, genotypes 1, 2, 3, 4, 5 and 6) and subtypes (including, but not limited to, subtypes 1a, 1b, 2a, 2b, 2c, 3a, 4a-4f, 5a and 6a) of HCV. For example, infectious nucleic acid sequence of the 2a strain HC-J6, described herein can be used to produce chimeras with sequences from the genomes of other strains of HCV from different genotypes or subtypes. Nucleic acid sequences which comprise sequences from two or more HCV genotypes or subtypes are designated "chimeric nucleic acid sequences".

The invention further relates to mutations of the infectious nucleic acid sequence of the invention where mutation includes, but is not limited to, point mutations, deletions and insertions. In one embodiment, a gene or fragment thereof can be deleted to determine the effect of the deleted gene or genes on the properties of the encoded virus such as its virulence and its ability to replicate. In an alternative embodiment, a mutation may be introduced into the infectious nucleic acid sequences to examine the effect of the mutation on the properties of the virus.

The invention also relates to the introduction of mutations or deletions into the infectious nucleic acid sequence in order to produce an attenuated hepatitis C virus suitable for vaccine development.

The invention further relates to the use of the infectious nucleic acid sequence to produce attenuated viruses via passage _in vitro_ or _in vivo_ of the viruses produced by transfection of a host cell with the infectious nucleic acid sequence.

The present invention also relates to the use of the nucleic acid sequence of the invention or fragments thereof in the production of polypeptides where "nucleic acid sequence of the invention" refers to infectious nucleic acid sequence, mutations of infectious nucleic acid sequence, chimeric nucleic acid sequence and sequences which comprise the genome of attenuated viruses produced from the infectious nucleic acid sequence of the invention. In one embodiment, said polypeptide or polypeptides are fully or partially purified from hepatitis C virus produced by cells transfected with nucleic acid sequence of the invention.

In another embodiment, the polypeptide or polypeptides are produced recombinantly from a fragment of the nucleic acid sequences of the invention. In yet another embodiment, the polypeptides are chemically synthesized.

The polypeptides of the invention, especially structural polypeptides, can serve as immunogens in the development of vaccines or as antigens in the development of diagnostic assays for detecting the presence of HCV in biological samples.

The invention therefore also relates to vaccines for use in immunizing mammals especially humans against hepatitis C. In one embodiment, the vaccine comprises one or more polypeptides made from the nucleic acid sequence of the invention or fragment thereof. In a second embodiment, the vaccine comprises a hepatitis C virus produced by transfection of host cells with the nucleic acid sequences of the invention.

The present invention therefore relates to methods for preventing hepatitis C in a mammal. In one embodiment the method comprises administering to a mammal a polypeptide or polypeptides encoded by the nucleic acid sequence of the invention in an amount effective to induce protective immunity to hepatitis C. In another embodiment, the method of prevention comprises administering to a mammal a hepatitis C virus of the invention in an amount effective to induce protective immunity against hepatitis C.

In yet another embodiment, the method of protection comprises administering to a mammal the nucleic acid sequence of the invention or a fragment thereof in an amount effective to induce protective immunity against hepatitis C.

The invention also relates to hepatitis C viruses produced by host cells transfected with the nucleic acid sequence of the present invention.

The invention therefore also provides pharmaceutical compositions comprising the nucleic acid sequence of the invention and/or the encoded hepatitis C viruses. The invention further provides pharmaceutical compositions comprising polypeptides encoded by the nucleic acid sequence of the invention or fragments thereof. The pharmaceutical compositions of the invention may be used prophylactically or therapeutically.

The invention also relates to antibodies to the hepatitis C virus of the invention or their encoded polypeptides and to pharmaceutical compositions comprising these antibodies.

The invention also relates to the use of the nucleic acid sequences of the invention to identify cell lines capable of supporting the replication of HCV _in vitro_.

The invention further relates to the use of the nucleic acid sequences of the invention or their encoded viral enzymes (e.g. NS3 serine protease, NS3 helicase, NS5B RNA polymerase) to develop screening assays to identify antiviral agents for HCV.

Brief Description Of Figures

Figure 1 shows the amplification and cloning of hepatitis C virus genotype 2a (strain HC-J6$_{Ch}$). The nucleotide positions correspond to the sequence of PJ6CF, a full length cDNA clone of hepatitis C virus, genotype 2a, strain HC-J6$_{CH}$. Products from polymerase

chain reaction are also shown. The names of the clones obtained from these products are indicated (number of clones sequenced are shown in parenthesis). The composition of the full-length cDNA clone is shown at the bottom. The restriction enzymes used for cloning are indicated. An *Xba*I site in HC-J6$_{CH}$ was eliminated by a silent substitution at position 5494.

Figure 2 shows tree analysis of clones amplified from an infectious acute phase plasma pool generated in a chimpanzee inoculated with human plasma containing strain HC-J6 (Okamoto *et al.*, 1991) as well as a tree of the predicted polyprotein sequence of HC-J6$_{CH}$ and the infectious HC-J6$_{CH}$ cDNA clone (pJ6CF). The nucleotide positions with deletions or insertions were stripped in the analysis of the clones. Multiple sequence alignments and tree analyses were performed with GeneWorks (Oxford Molecular Group) (Bukh *et al.*, 1995). Genotype designations are indicated. Other sequences included in the analysis are HC-J8 (Okamoto *et al.*, 1992), genotype 1a infectious clone BEBE1 (Nakao *et al.*, 1996), H77C (Yanagi *et al.*, 1997); genotype 1b infectious clone J4L6S (Yanagi *et al.*, 1998). The scale in each tree indicates the calculated genetic distance.

Figure 3 shows the alignment of the hypervariable region 1 sequences from 8 J6S clones of strain HC-J6$_{CH}$. HC-J6$_{CH}$ represents the consensus amino acid sequence of the infectious plasma pool from an experimentally infected chimpanzee. HC-J6 is the published amino acid sequence of the original inoculum (Okamoto *et al.*, 1991).

Figure 4 shows the construction of four intertypic chimeric cDNA clones. White boxes are

sequences derived from genotype 2a clone pJ6CF, and black boxes are sequences derived from genotype 1a clone pCV-H77C (Yanagi *et al.*, 1997). An *Nde*I site (mutation at position 9158 of pCV-H77C) was eliminated and an artificial *Nde*I site (mutation at position 2765 of pCV-H77C) was created by site-directed mutagenesis; silent mutations are underlined.

Figures 5A and 5B show the alignment of the nucleotide sequences of the 5' (Fig. 5A) and 3' UTRs (Fig. 5B) and the amino acid sequences of E2/p7/NS2 junctions (Fig. 5B) in the intertypic 1a, 2a chimeric cDNA clones. In the 5' UTR alignment, the first 39 nts of core believed to be important for the IRES function were included (Lemon and Honda, 1997). Top line: the sequence of the infectious genotype 1a clone pCV-H77C (Yanagi *et al.*, 1997). Bottom line: the sequence of the infectious genotype 2a clone pJ6CF. Dot: identity with the sequence of H77C. Capital letter: different from the sequence of H77C. Dash: deletion. Bold face: initiation or stop codon of the ORF. Underlined: *Age*I cleavage site. Arrow: putative sites in the HCV polyprotein cleaved by host signal peptidases. Numbering corresponds to the sequence of pCV-H77C.

Figures 6A-6F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1a strain H77C and Figures 6G-6H show the amino acid sequence encoded by the clone.

Figures 7A-7F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1b strain HC-J4 and Figures 7G-H show the amino acid sequence encoded by the clone.

DESCRIPTION OF THE INVENTION

The present invention relates to nucleic acid sequence which comprises the genome of an infectious hepatitis C virus. More specifically, the invention relates to nucleic acid sequence which encodes infectious hepatitis C virus of strain HC-$J6_{CH}$, genotype 2a. The infectious nucleic acid sequence of the invention is shown in SEQ ID NO:1 and is contained in a plasmid construct deposited with the American Type Culture Collection (ATCC) on May 28, 1999 and having ATCC accession number PTA-153.

The invention also relates to "chimeric nucleic acid sequences" where the chimeric nucleic acid sequences consist of open-reading frame sequences and/or 5′ and/or 3′ untranslated sequences taken from nucleic acid sequences of hepatitis C viruses of different genotypes or subtypes.

In one embodiment, the chimeric nucleic acid sequence consists of sequence from the genome of infectious HCV of genotype 2a which encodes structural polypeptides and sequence from the genome of a HCV of a different genotype or subtype which encodes nonstructural polypeptides.

Alternatively, the nonstructural region of infectious HCV of genotype 2a and structural region of a HCV of a different genotype or subtype may be combined. This will result in a chimeric nucleic acid sequence consisting of sequence from the genome of infectious HCV of genotype 2a which encodes nonstructural polypeptides and sequence from the genome of a HCV of a another genotype or subtype which encodes structural polypeptides.

Preferably, the nucleic acid sequence from the genome of the infectious HCV clone of genotype 1a (deposited with the ATCC on June 2, 1999 ; Figures 6A-6F), or the nucleic acid sequence from the genome of the infectious HCV clone of genotype 1b (ATCC accession number 209596; Figures 7A-7F) is used to construct the chimeric nucleic acid sequence with the HCV of genotype 2a of the invention.

It is believed that the construction of such chimeric nucleic acid sequences will be of importance in studying the growth and virulence properties of hepatitis C virus and in the production of candidate hepatitis C virus vaccines suitable to confer protection against multiple genotypes of HCV. For example, one might produce a "multivalent" vaccine by putting epitopes from several genotypes or subtypes into one clone. Alternatively one might replace just a single gene from an infectious sequence with the corresponding gene from the genomic sequence of a strain from another genotype or subtype or create a chimeric gene which contains portions of a gene from two genotypes or subtypes. Examples of genes which could be replaced or which could be made chimeric, include, but are not limited to, the E1, E2 and NS4 genes.

The invention further relates to mutations of the infectious nucleic acid sequences where "mutations" include, but are not limited to, point mutations, deletions and insertions. Of course, one of ordinary skill in the art would recognize that the size of the insertions would be limited by the ability of the resultant nucleic acid sequence to be properly packaged within the virion. Such mutations could be produced by

techniques known to those of skill in the art such as site-directed mutagenesis, fusion PCR, and restriction digestion followed by religation.

In one embodiment, mutagenesis might be undertaken to determine sequences that are important for viral properties such as replication or virulence. For example, one may introduce a mutation into the infectious nucleic acid sequence which eliminates the cleavage site between the NS4A and NS4B polypeptides to examine the effects on viral replication and processing of the polypeptide.

Alternatively, one may delete all or part of a gene or of the 5′ or 3′ nontranslated region contained in an infectious nucleic acid sequence and then transfect a host cell (animal or cell culture) with the mutated sequence and measure viral replication in the host by methods known in the art such as RT-PCR. Preferred genes include, but are not limited to, the P7, NS4B and NS5A genes. Of course, those of ordinary skill in the art will understand that deletion of part of a gene, preferably the central portion of the gene, may be preferable to deletion of the entire gene in order to conserve the cleavage site boundaries which exist between proteins in the HCV polyprotein and which are necessary for proper processing of the polyprotein.

In the alternative, if the transfection is into a host animal such as a chimpanzee, one can monitor the virulence phenotype of the virus produced by transfection of the mutated infectious nucleic acid sequence by methods known in the art such as measurement of liver enzyme levels (alanine aminotransferase (ALT) or isocitrate dehydrogenase (ICD)) or by histopathology

of liver biopsies. Thus, mutations of the infectious nucleic acid sequences may be useful in the production of attenuated HCV strains suitable for vaccine use.

The invention also relates to the use of the infectious nucleic acid sequence of the present invention to produce attenuated viral strains via passage in vitro or in vivo of the virus produced by transfection with the infectious nucleic acid sequence.

The present invention therefore relates to the use of the nucleic acid sequence of the invention to identify cell lines capable of supporting the replication of HCV.

In particular, it is contemplated that the mutations of the infectious nucleic acid sequence of the invention and the production of chimeric sequences as discussed above may be useful in identifying sequences critical for cell culture adaptation of HCV and hence, may be useful in identifying cell lines capable of supporting HCV replication.

Transfection of tissue culture cells with the nucleic acid sequences of the invention may be done by methods of transfection known in the art such as electroporation, precipitation with DEAE-Dextran or calcium phosphate or liposomes.

In one such embodiment, the method comprises the growing of animal cells, especially human cells, in vitro and transfecting the cells with the nucleic acid of the invention, then determining if the cells show indicia of HCV infection. Such indicia include the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the detection of viral polypeptides by Western blotting

using antibodies specific therefor; and the detection of newly transcribed viral RNA within the cells via methods such as RT-PCR. The presence of live, infectious virus particles following such tests may also be shown by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of HCV infection.

Suitable cells or cell lines for culturing HCV include, but are not limited to, lymphocyte and hepatocyte cell lines known in the art.

Alternatively, primary hepatocytes can be cultured, and then infected with HCV; or, the hepatocyte cultures could be derived from the livers of infected chimpanzees. In addition, various immortalization methods known to those of ordinary skill in the art can be used to obtain cell lines derived from hepatocyte cultures. For example, primary hepatocyte cultures may be fused to a variety of cells to maintain stability.

The present invention further relates to the *in vitro* and *in vivo* production of hepatitis C viruses from the nucleic acid sequences of the invention.

In one embodiment, the sequences of the invention can be inserted into an expression vector that functions in eukaryotic cells. Eukaryotic expression vectors suitable for producing high efficiency gene transfer *in vivo* are well known to those of ordinary skill in the art and include, but are not limited to, plasmids, vaccinia viruses, retroviruses, adenoviruses and adeno-associated viruses.

In another embodiment, the sequences contained in the recombinant expression vector can be transcribed *in vitro* by methods known to those of ordinary skill in

the art in order to produce RNA transcripts which encode the hepatitis C viruses of the invention. The hepatitis C viruses of the invention may then be produced by transfecting cells by methods known to those of ordinary skill in the art with either the in vitro transcription mixture containing the RNA transcripts or with the recombinant expression vectors containing the nucleic acid sequences described herein.

The hepatitis C viruses produced from the sequences of the invention may be purified or partially purified from the transfected cells by methods known to those of ordinary skill in the art. In a preferred embodiment, the viruses are partially purified prior to their use as immunogens in the pharmaceutical compositions and vaccines of the present invention.

The present invention therefore relates to the use of the hepatitis C viruses produced from the nucleic acid sequences of the invention as immunogens in live or killed (e.g., formalin inactivated) vaccines to prevent hepatitis C in a mammal.

In an alternative embodiment, the immunogen of the present invention may be an infectious nucleic acid sequence, a chimeric nucleic acid sequence, or a mutated infectious nucleic acid sequence which encodes a hepatitis C virus. Where the sequence is a cDNA sequence, the cDNAs and their RNA transcripts may be used to transfect a mammal by direct injection into the liver tissue of the mammal as described in the Examples.

Alternatively, direct gene transfer may be accomplished via administration of a eukaryotic expression vector containing a nucleic acid sequence of the invention.

In yet another embodiment, the immunogen may be a polypeptide encoded by the nucleic acid sequences of the invention. The present invention therefore also relates to polypeptides produced from the nucleic acid sequences of the invention or fragments thereof. In one embodiment, polypeptides of the present invention can be recombinantly produced by synthesis from the nucleic acid sequences of the invention or isolated fragments thereof, and purified, or partially purified, from transfected cells using methods already known in the art. In an alternative embodiment, the polypeptides may be purified or partially purified from viral particles produced via transfection of a host cell with the nucleic acid sequences of the invention. Such polypeptides might, for example, include either capsid or envelope polypeptides prepared from the sequences of the present invention.

When used as immunogens, the nucleic acid sequences of the invention, or the polypeptides or viruses produced therefrom, are preferably partially purified prior to use as immunogens in pharmaceutical compositions and vaccines of the present invention. When used as a vaccine, the sequences and the polypeptide and virus products thereof, can be administered alone or in a suitable diluent, including, but not limited to, water, saline, or some type of buffered medium. The vaccine according to the present invention may be administered to an animal, especially a mammal, and most especially a human, by a variety of routes, including, but not limited to, intradermally, intramuscularly, subcutaneously, or in any combination thereof.

Suitable amounts of material to administer for prophylactic and therapeutic purposes will vary depending on the route selected and the immunogen (nucleic acid, virus, polypeptide) administered. One skilled in the art will appreciate that the amounts to be administered for any particular treatment protocol can be readily determined without undue experimentation. The vaccines of the present invention may be administered once or periodically until a suitable titer of anti-HCV antibodies appear in the blood. For an immunogen consisting of a nucleic acid sequence, a suitable amount of nucleic acid sequence to be used for prophylactic purposes might be expected to fall in the range of from about 100 µg to about 5 mg and most preferably in the range of from about 500 µg to about 2mg. For a polypeptide, a suitable amount to use for prophylactic purposes is preferably 100 ng to 100 µg and for a virus 10^2 to 10^6 infectious doses. Such administration will, of course, occur prior to any sign of HCV infection.

A vaccine of the present invention may be employed in such forms as capsules, liquid solutions, suspensions or elixirs for oral administration, or sterile liquid forms such as solutions or suspensions. An inert carrier is preferably used, such as saline or phosphate-buffered saline, or any such carrier in which the HCV of the present invention can be suitably suspended. The vaccines may be in the form of single dose preparations or in multi-dose flasks which can be utilized for mass-vaccination programs of both animals and humans. For purposes of using the vaccines of the present invention reference is made to Remington's

Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., Osol (Ed.) (1980); and New Trends and Developments in Vaccines, Voller et al. (Eds.), University Park Press, Baltimore, Md. (1978), both of which provide much useful information for preparing and using vaccines. Of course, the polypeptides of the present invention, when used as vaccines, can include, as part of the composition or emulsion, a suitable adjuvant, such as alum (or aluminum hydroxide) when humans are to be vaccinated, to further stimulate production of antibodies by immune cells. When nucleic acids, viruses or polypeptides are used for vaccination purposes, other specific adjuvants such as CpG motifs (Krieg, A.K. et al.(1995) and (1996)), may prove useful.

When the nucleic acids, viruses and polypeptides of the present invention are used as vaccines or inocula, they will normally exist as physically discrete units suitable as a unitary dosage for animals, especially mammals, and most especially humans, wherein each unit will contain a predetermined quantity of active material calculated to produce the desired immunogenic effect in association with the required diluent. The dose of said vaccine or inoculum according to the present invention is administered at least once. In order to increase the antibody level, a second or booster dose may be administered at some time after the initial dose. The need for, and timing of, such booster dose will, of course, be determined within the sound judgment of the administrator of such vaccine or inoculum and according to sound principles well known in the art. For example, such booster dose could reasonably be expected to be advantageous at some time

between about 2 weeks to about 6 months following the initial vaccination. Subsequent doses may be administered as indicated.

The nucleic acid sequences, viruses and polypeptides of the present invention can also be administered for purposes of therapy, where a mammal, especially a primate, and most especially a human, is already infected, as shown by well known diagnostic measures. When the nucleic acid sequences, viruses or polypeptides of the present invention are used for such therapeutic purposes, much of the same criteria will apply as when it is used as a vaccine, except that inoculation will occur post-infection. Thus, when the nucleic acid sequences, viruses or polypeptides of the present invention are used as therapeutic agents in the treatment of infection, the therapeutic agent comprises a pharmaceutical composition containing a sufficient amount of said nucleic acid sequences, viruses or polypeptides so as to elicit a therapeutically effective response in the organism to be treated. Of course, the amount of pharmaceutical composition to be administered will, as for vaccines, vary depending on the immunogen contained therein (nucleic acid, polypeptide, virus) and on the route of administration.

The therapeutic agent according to the present invention can thus be administered by subcutaneous, intramuscular or intradermal routes. One skilled in the art will certainly appreciate that the amounts to be administered for any particular treatment protocol can be readily determined without undue experimentation. Of course, the actual amounts will vary depending on the route of administration as well as the sex, age, and

clinical status of the subject which, in the case of human patients, is to be determined with the sound judgment of the clinician.

The therapeutic agent of the present invention can be employed in such forms as capsules, liquid solutions, suspensions or elixirs, or sterile liquid forms such as solutions or suspensions. An inert carrier is preferably used, such as saline, phosphate-buffered saline, or any such carrier in which the HCV of the present invention can be suitably suspended. The therapeutic agents may be in the form of single dose preparations or in the multi-dose flasks which can be utilized for mass-treatment programs of both animals and humans. Of course, when the nucleic acid sequences, viruses or polypeptides of the present invention are used as therapeutic agents they may be administered as a single dose or as a series of doses, depending on the situation as determined by the person conducting the treatment.

The nucleic acids, polypeptides and viruses of the present invention can also be utilized in the production of antibodies against HCV. The term "antibody" is herein used to refer to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules. Examples of antibody molecules are intact immunoglobulin molecules, substantially intact immunoglobulin molecules and portions of an immunoglobulin molecule, including those portions known in the art as Fab, $F(ab')_2$ and F(v) as well as chimeric antibody molecules.

Thus, the polypeptides, viruses and nucleic acid sequences of the present invention can be used in

the generation of antibodies that immunoreact (i.e., specific binding between an antigenic determinant-containing molecule and a molecule containing an antibody combining site such as a whole antibody molecule or an active portion thereof) with antigenic determinants on the surface of hepatitis C virus particles.

The present invention therefore also relates to antibodies produced following immunization with the nucleic acid sequences, viruses or polypeptides of the present invention. These antibodies are typically produced by immunizing a mammal with an immunogen or vaccine to induce antibody molecules having immunospecificity for polypeptides or viruses produced in response to infection with the nucleic acid sequences of the present invention. When used in generating such antibodies, the nucleic acid sequences, viruses, or polypeptides of the present invention may be linked to some type of carrier molecule. The resulting antibody molecules are then collected from said mammal. Antibodies produced according to the present invention have the unique advantage of being generated in response to authentic, functional polypeptides produced according to the actual cloned HCV genome.

The antibody molecules of the present invention may be polyclonal or monoclonal. Monoclonal antibodies are readily produced by methods well known in the art. Portions of immunoglobin molecules, such as Fabs, as well as chimeric antibodies, may also be produced by methods well known to those of ordinary skill in the art of generating such antibodies.

The antibodies according to the present invention may also be contained in blood, plasma, serum, hybridoma supernatants, and the like. Alternatively, the antibody of the present invention is isolated to the extent desired by well known techniques such as, for example, using DEAE Sephadex. The antibodies produced according to the present invention may be further purified so as to obtain specific classes or subclasses of antibody such as IgM, IgG, IgA, and the like. Antibodies of the IgG class are preferred for purposes of passive protection.

The antibodies of the present invention are useful in the prevention and treatment of diseases caused by hepatitis C virus in animals, especially mammals, and most especially humans.

In providing the antibodies of the present invention to a recipient mammal, preferably a human, the dosage of administered antibodies will vary depending on such factors as the mammal's age, weight, height, sex, general medical condition, previous medical history, and the like.

In general, it will be advantageous to provide the recipient mammal with a dosage of antibodies in the range of from about 1 mg/kg body weight to about 10 mg/kg body weight of the mammal, although a lower or higher dose may be administered if found desirable. Such antibodies will normally be administered by intravenous or intramuscular route as an inoculum. The antibodies of the present invention are intended to be provided to the recipient subject in an amount sufficient to prevent, lessen or attenuate the severity, extent or duration of any existing infection.

The antibodies prepared by use of the nucleic acid sequences, viruses or polypeptides of the present invention are also highly useful for diagnostic purposes. For example, the antibodies can be used as in vitro diagnostic agents to test for the presence of HCV in biological samples taken from animals, especially humans. Such assays include, but are not limited to, radioimmunoassays, EIA, fluorescence, Western blot analysis and ELISAs. In one such embodiment, the biological sample is contacted with antibodies of the present invention and a labeled second antibody is used to detect the presence of HCV to which the antibodies are bound.

Such assays may be, for example, direct where the labeled first antibody is immunoreactive with the antigen, such as, for example, a polypeptide on the surface of the virus; indirect where a labeled second antibody is reactive with the first antibody; a competitive protocol such as would involve the addition of a labeled antigen; or sandwich where both labeled and unlabeled antibody are used, as well as other protocols well known and described in the art.

In one embodiment, an immunoassay method would utilize an antibody specific for HCV envelope determinants and would further comprise the steps of contacting a biological sample with the HCV-specific antibody and then detecting the presence of HCV material in the test sample using one of the types of assay protocols as described above. Polypeptides and antibodies produced according to the present invention may also be supplied in the form of a kit, either present in vials as purified material, or present in

compositions and suspended in suitable diluents as previously described.

In a preferred embodiment, such a diagnostic test kit for detection of HCV antigens in a test sample comprises in combination a series of containers, each container a reagent needed for such assay. Thus, one such container would contain a specific amount of HCV-specific antibody as already described, a second container would contain a diluent for suspension of the sample to be tested, a third container would contain a positive control and an additional container would contain a negative control. An additional container could contain a blank.

For all prophylactic, therapeutic and diagnostic uses, the antibodies of the invention and other reagents, plus appropriate devices and accessories, may be provided in the form of a kit so as to facilitate ready availability and ease of use.

The present invention also relates to the use of nucleic acid sequences and polypeptides of the present invention to screen potential antiviral agents for antiviral activity against HCV. Such screening methods are known by those of skill in the art. Generally, the antiviral agents are tested at a variety of concentrations, for their effect on preventing viral replication in cell culture systems which support viral replication, and then for an inhibition of infectivity or of viral pathogenicity (and a low level of toxicity) in an animal model system.

In one embodiment, animal cells (especially human cells) transfected with the nucleic acid sequences of the invention are cultured <u>in vitro</u> and the cells are

treated with a candidate antiviral agent (a chemical, peptide etc.) by adding the candidate agent to the medium. The treated cells are then exposed, possibly under transfecting or fusing conditions known in the art, to the nucleic acid sequences of the present invention. A sufficient period of time would then be allowed to pass for infection to occur, following which the presence or absence of viral replication would be determined versus untreated control cells by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the detection of viral polypeptides by Western blotting using antibodies specific therefor; the detection of newly transcribed viral RNA within the cells by RT-PCR; and the detection of the presence of live, infectious virus particles by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of HCV infection. A comparison of results obtained for control cells (treated only with nucleic acid sequence) with those obtained for treated cells (nucleic acid sequence and antiviral agent) would indicate, the degree, if any, of antiviral activity of the candidate antiviral agent. Of course, one of ordinary skill in the art would readily understand that such cells can be treated with the candidate antiviral agent either before or after exposure to the nucleic acid sequence of the present invention so as to determine what stage, or stages, of viral infection and replication said agent is effective against.

In an alternative embodiment, viral enzyme such as NS3 protease, NS2-NS3 protease, NS3 helicase or NS5B RNA polymerase may be produced from a nucleic acid sequence of the invention and used to screen for inhibitors which may act as antiviral agents. The structural and nonstructural regions of the HCV genome, including nucleotide and amino acid locations, have been determined, for example, as depicted in Houghton, M. (1996), Fig. 1; and Major, M.E. et al. (1997), Table 2.

Such above-mentioned protease inhibitors may take the form of chemical compounds or peptides which mimic the known cleavage sites of the protease and may be screened using methods known to those of skill in the art (Houghton, M. (1996) and Major, M.E. et al. (1997)). For example, a substrate may be employed which mimics the protease's natural substrate, but which provides a detectable signal (e.g. by fluorimetric or colorimetric methods) when cleaved. This substrate is then incubated with the protease and the candidate protease inhibitor under conditions of suitable pH, temperature etc. to detect protease activity. The proteolytic activities of the protease in the presence or absence of the candidate inhibitor are then determined.

In yet another embodiment, a candidate antiviral agent (such as a protease inhibitor) may be directly assayed <u>in vivo</u> for antiviral activity by administering the candidate antiviral agent to a chimpanzee transfected with a nucleic acid sequence of the invention or infected with a virus of the invention and then measuring viral replication <u>in vivo</u> via methods such as RT-PCR. Of course, the chimpanzee may be treated with the candidate agent either before or after

transfection with the infectious nucleic acid sequence or infected with a virus of the invention so as to determine what stage, or stages, of viral infection and replication the agent is effective against.

The invention also provides that the nucleic acid sequences, viruses and polypeptides of the invention may be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

All scientific publication and/or patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

Materials and Methods

Source of HCV

An infectious plasma pool of HCV genotype 2a (HC-J6$_{CH}$) prepared from acute phase plasma of a chimpanzee experimentally inoculated with plasma from a Japanese patient infected with strain HC-J6 (Okamoto *et al.*, 1991) was used for cloning. An infectious cDNA clone of HCV strain H77, genotype 1a was also used (pCV-H77C; Yanagi *et al.*, 1997).

Amplification, cloning and sequence analysis

Viral RNA was extracted from 100 µl aliquots of the HC-J6$_{CH}$ plasma pool with the TRIzol system (GIBCO/BRL) (Yanagi *et al.*, 1997). Primers used in cDNA synthesis and PCR amplification were based on the genomic sequence of strain HC-J6 (Okamoto *et al.*, 1991) and from the conserved region (3'X) of the 3' UTR of HCV genotype 2a (Tanaka *et al.*, 1996) (Table 1). The RNA

was denatured at 65°C for 2 min, and cDNA was synthesized at 42°C for 1 hour with Superscript II reverse transcriptase (GIBCO/BRL) and specific reverse primers in 20 µl reaction volumes. The cDNA mixtures were treated with RNase H and RNase T1 (GIBCO/BRL) at 37°C for 20 min.

TABLE 1

Oligonucleotides used for amplification and cloning of strain HC-J6$_{CH}$, genotype 2a

Designation	Sequence (5' → 3')a
2427S-H77	ACTGGACACGGAGGTGGCCGCGTC
2426S-H77	TTGTTCTTGTCGGGTTAATGGCGC
2645R-H77	GGGTGTACTACACACATGAGTAAG
2832R-H77	AAGCGCCCCTAACTGATGATG
H2751SII	**CGTCATCGATA**CCTCAGCGGGCATATGCACTGGACACGGA
H2786R	GTCCAGTGCATATGCCCGCTGAGG
H2870R	CATGCACCAGCTGATATAGCGCTTGTAATATG
H7851S	TCCGTAGAGGAAGCTTGCAGCCTGACGCCC
H9140S (M)	CAGAGGAGGCAGGGTGCTATATGTGGCAAGTAC
H9173R (M)	GTACTTGCCACATATAGCAGCCCTGCCTCCTCTG
H9471R	**CGTCTCTAGA**CAGGAAATGGCTTAAGAGGCCGGAGTGTTTACC
J6-H2556S	TTATGGATGCTCATCTTGTTGGGCCAGGCCGAAGCAGCTTTGGAGAACCTCGTAATACT CAATGC
356RF-J6H	AGGATTTGTGCTCATGGTGCACGGTCTACGAG
1S-J6F[b]	**TTTTTTTTGCGGCCGC*TAATACGACTCACTATAG***ACCCGCCCCTAATAGG
333S-J6	CCGTGCACCATGAGCACAAATCCTAAACCTC
753R-J6	GGATGTACCCCATGAGGTCGGCAAAG
2543S-J6F	GTTTGCGCCTGCTTATGGATGCTCATCTTG
2787R-J6(26)	GCGTCATAAGCATATGCCTGTTGGGG
3329R-J6	CCCTCAGCACTGGAGTACATCTG
5487-J6F	**CGTCATGCATA**CCCCTAGGGCGGCTCTCATTGAAGAGGG
5518R-J6F	CGTCCCCTCTTCAATGAGAGCCGCTCTAGA
9251S-J6F	GCGGTGAAGACCAAGCTCAAACTCACTC
9305R-J6F	**AATCTAGAA**GGCGCGCTTCCGGCAATGGAGTGAGTTTGAGC
9310R-J6F	**CGTCTCTAGA**GGATAAATCCAGGAGGCGCGCTTCCGGC
9399S-J6F	TACTTTTTGTAGGGGTAGGCCTTTTCC
9464-J6F	**CGTCTCTAGA**GTGTAGCTAATGTGTGCCGCTCTA
9470(24)-J6	CTATGGAGTGTAGCTAATGTGTGC
J6-3' XR	**CGTCTCTAGA**CATGATCTGCAGAGAGACCAGTTACGGCACTCTCTGFCAGTCATGCGGC TCACGGACCTTTCACAGCTAGCCGTGACTAGGGCTAAGATGGAGCCACC

a HCV-specific sequences are shown in plain text, non HCV-specific sequences are shown in bold face, and cleavage sites used for cDNA cloning are underlined.

b The core sequence of the T7 promotor is shown in italics.

The strategy used to amplify and clone the full-length HC-J6$_{CH}$ sequence is shown in Fig. 1. Nucleotide positions correspond to those of the 2a

infectious clone (pJ6CF) that is described herein. The 5' end of HC-J6$_{CH}$ (nts. 17-297, excluding primer sequences) was amplified from 2 µl of cDNA synthesized with primer a-2 (Yanagi *et al.*, 1996). PCR was performed with *AmpliTaq Gold* DNA polymerase (Perkin-Elmer) as described previously (Yanagi *et al.*, 1996) using primers 1S-J6F and a-2. After purification, the amplified products were cloned into pGEM-T Easy vector (Promega) using standard procedures and 5 clones (pJ6-5'UTR) were sequenced.

The 3' end of HC-J6$_{CH}$ was amplified in 3 overlapping pieces. RT-PCR of a short fragment of NS5B (nts. 9279-9439) was performed with primers 9251S-J6F and 9464R-J6F as described above. The PCR products were cloned into pGEM-T Easy vector and sequence analysis was performed from 5 pJ6-3'F clones. A second region spanning from NS5B to the conserved region of the 3' UTR (nts. 9376-9629) was amplified in RT-nested PCR (external primers H9261F and H3'X58R, internal primers H9282F and H3'X45R) (Yanagi *et al.*, 1997). The amplified products were cloned into pGEM-9zf(-) by using *Hind*III and *Xba*I sites and 14 pJ6-3'VR clones were sequenced. The third fragment, which included the 3' terminal sequence was amplified with primers 9399S-J6F and J6-3'XR from one of the pJ6-3'VR clones, and cloned into one of the pJ6-3'F clones by using *Stu*I and *Xba*I sites (pJ6-3'X).

The ORF of HCV HC-J6$_{CH}$ was amplified by long RT-PCR in 3 overlapping pieces. The amplification was performed on 2 µl of the cDNA mixtures with the Advantage cDNA polymerase mix (Clontech) (Yanagi *et al.*, 1997). The J6S fragment (nts. 86-2761) was amplified

with primers a-1 (Yanagi et al., 1996) and J6-2787R from cDNA synthesized with primer J6-3329R. A single PCR round was performed in a Robocycler thermal cycler (Stratagene), and consisted of denaturation at 99°C for 35 sec, annealing at 67°C for 30 sec and elongation at 68°C for 4 min 30 sec during the first 5 cycles, 5 min during the next 10 cycles, 5 min 30 sec during the following 10 cycles and 6 min during the last 10 cycles. The J6B fragment (nts. 2573-5488) was amplified with primers 2543S-J6F and 5518R-J6F from cDNA synthesized with primer 5518R-J6F. Finally, the J6A fragment (nts. 5515-9282) was amplified with primers 5487S-J6F and 9310R-J6F from cDNA synthesized with primer 9470R(24)-J6F. PCR amplifications of fragments J6B and J6A consisted of denaturation at 99°C for 35 sec, annealing at 67°C for 30 sec and elongation at 68°C for 6 min during the first 5 cycles, 7 min during the next 10 cycles, 8 min during the following 10 cycles and 9 min during the last 10 cycles.

After purification of the long PCR products with QIAquick PCR purification kit (QIAGEN), A-tailing reactions were performed with *AmpliTaq* DNA polymerase (Perkin Elmer) at 72 °C for 1 hour. The gel-purified A-tailed PCR products were cloned into pCR2.1 vector (Invitrogen) or pGEM-T Easy vector (Promega). DH5-alpha competent cells (GIBCO BRL) were transformed and selected on LB agar plates containing 100 μg/ml ampicillin (SIGMA) and amplified in LB liquid cultures at 30°C for 18 - 20 hrs (Yanagi *et al.*, 1997). Midiprep was performed using Wizard *Plus* Midipreps DNA

Purification System (Promega). Multiple clones of the J6S, J6A and the J6B fragments were sequenced.

The consensus sequence of strain HC-J6$_{CH}$ (nts. 17-9629) was determined by direct sequencing of PCR products (nts. 297-3004 and nts. 4893-5762) and by sequence analysis of the TA clones (nts. 17-5488 and nts. 5515-9629)(Fig. 1). Both strands of DNA were sequenced in all cases. Analyses of genomic sequences, including multiple sequence alignments and tree analyses, were performed with GeneWorks (Oxford Molecular Group) (Bukh *et al.*, 1995).

Construction of chimeric cDNA clones of genotypes 1a & 2a

Four full-length intertypic chimeric cDNA clones were constructed (Figs. 4, 5A, 5B). In each clone the C, E1 and E2 genes encoded the consensus amino acid sequence of HC-J6$_{CH}$. The p7 protein was encoded either by the HC-J6$_{CH}$ or pCV-H77C consensus sequence, and the NS proteins were all encoded by pCV-H77C genes. To engineer these cDNA clones, an *Nde*I site from pCV-H77C was first eliminated by a silent substitution (C to T) at position 9158. In brief, two fragments were amplified from pCV-H77C with primers H7851S and H9173R(M) and with primers H9140S(M) and H9417R (Table 3), gel-purified and used for fusion PCR with primers H7851S and H9417R. The fusion PCR products were cloned into pCV-H77C by using *Hind*III and *Afl*II sites. A new artificial *Nde*I site was introduced by a silent substitution (C to T) at position 2765. PCR products, which were amplified from pCV-H77C with primer H2751SII containing artificial *Cla*I and NdeI sites and primer H2870R, were cloned into the modified pCV-H77C by using

*Cla*I and *Eco*47III sites. The final construct (pH77CV) was used as a cassette vector to construct the intertypic chimeric HCV cDNA clones.

The four chimeric cDNA clones were constructed as follows. pH77CV-J6S (nucleotide sequence shown in SEQ ID No:3 and amino acid sequence shown in SEQ ID No:4): The *Age*I/*Bsm*I fragment of clone J6S2 and the *Bsm*I/*Nde*I fragment of clone J6S1, were cloned into pH77CV by using *Age*I and *Nde*I sites; pH77 (p7)CV-J6S (nucleotide sequence shown in SEQ ID No:5 and amino acid sequence shown in SEQ ID No:6): A fragment of pH77CV-J6S was replaced with a fragment amplified from pCV-H77C with primers J6-H2556S and H2786R by using *BsaB*I and *Nde*I sites; J6S (nucleotide sequence shown in SEQ ID No:7 and amino acid sequence shown in SEQ ID No:8): A fragment amplified from pH77pCV-H77C with primers a-1 and 356RF-J6H77 and another fragment amplified from pH77CV-J6S with primers 333S-J6 and 753R-J6 were gel-purified and a fusion-PCR was performed with primers a-1 and 753R-J6. The *Age*I/*Cla*I fragment of the subcloned fusion PCR products and the *Cla*I/*Nde*I fragment of pH77CV-J6S were cloned into pH77CV-J6S by using *Age*I and *Nde*I sites; pH77(p7)-J6S (nucleotide sequence shown in SEQ ID No:9 and amino acid sequence shown in SEQ ID No:10): The AgeI/ClaI fragment of J6S and the *Cla*I/*Nde*I fragment of (p7)CV-J6S were cloned into pH77(p7)CV-J6S by using *Age*I and *Nde*I sites.

Each intertypic chimeric cDNA clone was retransformed to select a single clone, and large-scale preparation of plasmid DNA was performed with a QIAGEN plasmid Maxi kit as described previously (Yanagi *et al.*, 1997). Each of the four cDNA clones was completely

sequenced before inoculation. Each clone was genetically stable since the digestion pattern was as expected following retransformation and the complete sequence was the expected one.

Construction of full-length cDNA clone HC-$J6_{CH}$

An overview of the full-length HC-$J6_{CH}$ clone is presented in Fig. 1. In the final construct pJ6CF, which encodes the consensus polyprotein of HC-$J6_{CH}$, an *Xba*I site was eliminated by a silent substitution (A to G) at position 5494. Digested fragments containing the consensus sequence were purified from the appropriate subclones and ligated using the sites indicated. The full-length cDNA clone (pJ6CF) was retransformed to select a single clone, and large-scale preparation of plasmid DNA followed by the complete sequence analysis was performed. Clone pJ6CF was genetically stable.

Intrahepatic transfection of chimpanzee with transcribed RNA

In duplicate 100 µl reactions, RNA was transcribed *in vitro* with T7 RNA polymerase (Promega) from 10 µg of template plasmid linearized with *Xba*I (Promega) as described previously (Yanagi *et al.*, 1997). The integrity of the RNA was checked by electrophoresis through agarose gel stained with ethidium bromide (Yanagi *et al.*, 1997). Each transcription mixture was diluted with 400 µl of ice-cold phosphate-buffered saline without calcium or magnesium and then immediately frozen on dry ice and stored at -80°C. Within 24 hours, both transcription mixtures were injected into the same chimpanzee by percutaneous intrahepatic injection guided by ultrasound (Yanagi *et al.*, 1998, 1999). If the

chimpanzee did not become infected, the same transfection was repeated once. After two negative results, the next clone was inoculated into the same chimpanzee following the same protocol. Injections were performed at weeks 0 and 2 with pH77CV-J6S, at weeks 5 and 8 with pH77(p7)CV-J6S, at weeks 14 and 16 with pH77-J6S, at weeks 19 and 23 with pH77(p7)-J6S, at week 28 with pJ6CF, and finally at week 34 with pCV-H77C. The chimpanzee was maintained under conditions that met or exceeded all requirements for its use in an approved facility.

Serum samples were collected weekly from the chimpanzee and monitored for liver enzyme levels by standard procedures, anti-HCV antibodies by the second-generation ELISA (Abbott) and HCV RNA by a sensitive RT-nested PCR assay with *AmpliTaq Gold* DNA polymerase using primers from the 5' UTR (Yanagi *et al.*, 1996). Samples were scored as negative for HCV RNA if two independent tests on 100 µl of serum were negative. The genome equivalent (GE) titer of HCV in positive samples was determined by RT-nested PCR on 10-fold serial dilutions of the extracted RNA (Bukh *et al.*, 1998). The consensus sequence of the complete ORF from the chimpanzee infected with RNA transcripts of pJ6CF was determined by direct sequencing of overlapping PCR products obtained by long RT-nested PCR as previously described (Yanagi *et al.*, 1997) with HC-J6 specific primers. After the intrahepatic transfection with RNA transcripts of pCV-H77C, we performed H77(genotype 1a)-specific RT-nested PCR with primers 2427S-H77 and 2832R-H77 for the 1st round and with primers 2462S-H77 and 2645R-H77 for the 2nd round (Table 3). The

sensitivity of this assay was equivalent to that of the assay using 5' UTR primers when testing serum containing only H77, genotype 1a. The genome titer of genotype 1a was determined by using this specific RT- nested PCR on 10-fold serial dilutions of the extracted RNA.

EXAMPLE 1

Sequence analysis of HCV strain HC-J6$_{CH}$

As minor deviations from the consensus amino acid sequence were found previously to render full-length HCV cDNA clones noninfectious (Yanagi *et al.*, 1997, 1998), the consensus sequence of the cloning source of genotype 2a (strain HC-J6$_{CH}$) was determined prior to constructing any full-length clones. In brief, a plasma pool containing strain HC-J6$_{CH}$ was prepared from acute phase plasmapheresis units collected from a chimpanzee experimentally infected with HC-J6 (Okamoto *et al.*, 1991). The HCV genome titer of this pool was $10^{5.4}$ genome equivalents (GE)/ml (Quantiplex HCV RNA bDNA 2.0, Chiron) and the infectivity titer was 10^4 chimpanzee infectious doses/ml.

The consensus sequence of the 5' UTR of HC-J6$_{CH}$ (nts. 17-340) was deduced from 5 clones containing nts. 17-297 and 8 clones containing nts. 86-340. The 5' UTR of the various clones was highly conserved, but the consensus sequence of HC-J6$_{CH}$ differed by 2 nucleotides from that published previously for HC-J6 (Okamoto *et al.*, 1991: C to T at position 36 and T to C at position 222).

The consensus sequence of 14 clones of the 3' UTR of HC-J6$_{CH}$ indicated that the 39 nucleotide long variable region was highly conserved in this strain and

was identical to that previously published for HC-J6 (Okamoto *et al.*, 1991). The polypyrimidine tract varied greatly in length (84-164 nucleotides), and contained some conserved A residues. In the conserved region, the proximal 16 nucleotides were identical to those previously published for isolates of different HCV genotypes (Kolykhalov *et al.*, 1996; Tanaka *et al.*, 1996; Yamada *et al.*, 1996). The remaining 82 nucleotides of the conserved region were determined for other genotype 2a strains (Tanaka *et al.*, 1996) but not for HC-J6 or HC-$J6_{CH}$.

The ORF of HC-$J6_{CH}$ was amplified in 3 fragments by RT-PCR (Fig. 1). Eight clones of the J6S fragment (nts. 86-2761), 6 clones of the J6B fragment (nts. 2573-5488) and 6 clones of the J6A fragment (nts. 5515-9298) were sequenced. PCR fragments containing nts. 5489-5514 were sequenced directly. A quasispecies was found at 243 nucleotide (2.7%) and 69 amino acid (2.3%) positions, scattered throughout the 9099 nts (3033 aa) of the ORF. However, the majority, 231 nucleotide substitutions, were detected only once and 71.6 % of these represented silent mutations. The 12 remaining nucleotide substitutions were each restricted to 2 clones and only 4 of these resulted in amino acid changes. The nucleotide difference among the J6S clones ranged from 0.1 - 1.3%, among the J6B clones it ranged from 0.1 - 0.3%, and it ranged from 0.2 - 4.0% among the J6A clones (Fig. 2). Three of 8 J6S clones, 4 of 6 J6B clones, and all 6 J6A clones had defective polyproteins due to nucleotide deletions, insertions or substitutions.

The sequences of clones of strain HC-J6$_{CH}$ were relatively homogeneous. This was highlighted by the high degree of conservation among clones of the HVR1 (Fig. 3), a region frequently used to study the quasispecies of HCV (Bukh *et al.*, 1995). An exception was the sequence of clone J6A1, which differed by about 4% from the other clones of this region (Fig. 2). Importantly, the consensus sequence of strain HC-J6$_{CH}$ (nts. 17-9629) could be determined with no ambiguity at the nucleotide or deduced amino acid level. The difference between the consensus ORF sequence of HC-J6$_{CH}$ from the experimentally infected chimpanzee and that of HC-J6 of the inoculum (Okamoto *et al.*, 1991) was 4.1 % and 2.2 % at the nucleotide and deduced amino acid levels, respectively (Fig. 2, Table 2). Moreover, we found that 12 (44.4%) of the 27 amino acids constituting HVR1 differed between HC-J6$_{CH}$ and HC-J6 (Fig. 3). Such diversities are greater than the < 2 % generally considered to comprise a quasispecies. In fact, these differences are equivalent to those found between the two prototype strains of HCV genotype 1a [strains HCV-1 (Choo *et al.*, 1991) and H77 (Yanagi *et al.*, 1997)]. These results indicated that HC-J6$_{CH}$, which represented the major species in the experimentally infected chimpanzee, was a minor species in the original inoculum.

TABLE 2

Percent difference of nucleotide and predicted amino acid sequences between strain HC-J6 (Okamoto *et al.*, 1991) and strain HC-J6$_{CH}$ from acute phase plasma pool of a chimpanzee inoculated with HC-J6

Genome Region	nt.position[a]	% nt. difference	% a.a. difference
ORF	341-9439	4.1 (373/9099)[b]	2.2 (66/3033)[b]
5' UTR	17-340	0.6 (2/324)	
Core	341-913	0.5 (3/573)	0 (0/191)
E1	914-1489	4.3 (25/576)	2.1 (4/192)
HVR1	1490-1570	24.7 (20/81)	44.4 (12/27)
E2-$_{HVR1}$	1571-2590	3.9 (40/1020)	3.2 (11/340)
p7	2591-2779	3.7 (7/189)	3.2 (2/63)
NS2	2780-3430	4.0 (26/651)	2.8 (6/217)
NS3	3431-5323	4.0 (76/1893)	0.8 (5/631)
NS4A	5324-5485	4.3 (7/162)	1.9 (1/54)
NS4B	5486-6268	3.7 (29/783)	0.4 (1/261)
NS5A	6269-7666	5.4 (75/1398)	3.4 (16/466)
NS5B	7667-9439	3.7 (65/1773)	1.4 (8/591)
3' UTR	9440-9481	0 (0/42)	

a The nucleotide positions correspond to those of the infectious full-length genotype 2a clone (pJ6CF).

b The numbers in parenthesis indicate the nucleotide or amino acid differences for each region.

Example 2

Chimeric molecular clones

As chimeric flaviviruses with substituted structural genes have been useful in defining the biological function of viral sequences or proteins, in analyzing immune responses and in generating attenuated vaccine candidates (Bray and Lai, 1991; Chambers *et al.*, 1999; Pletnev *et al.*, 1992, 1993, 1998). The consensus sequence of the 2a structural genes and surrounding region was substituted for that of the infectious 1a cDNA clone. In the genotype 1a backbone, two silent mutations were introduced for cloning purposes [at positions 2765 (p7) and 9158 (NS5B) of pCV-H77C] (Fig. 4). The complete sequence of each chimera was verified. Infectivity of RNA transcripts from four different

intertypic chimeric clones (Figs. 4, 5A, 5B) was evaluated by consecutive intrahepatic transfections of a chimpanzee. Clones were considered not to be viable if viral RNA was not detected in the serum within two weeks of the repeat transfection. All chimeric clones contained the C, E1 and E2 genes of genotype 2a. The two chimeric clones tested initially differed from each other in that one had the p7 gene of 2a (pH77CV-J6S) and the other [pH77(p7)CV-J6S] the p7 gene of 1a. They differed from the two other clones in that the 186 nucleotides of the 5' UTR just upstream of the initiation codon were from the 2a genotype. Since neither clone containing the chimeric 5' UTR was infectious, the chimeric 5' UTR was replaced with the consensus genotype 1a 5' UTR to generate the two p7 varieties [pH77-J6S and pH77(p7)-J6S]. After consecutive transfection of the four clones, no HCV RNA, anti-HCV or ALT elevation was detected in the chimpanzee during 28 weeks of follow-up, suggesting that RNA transcripts from these intertypic chimeric clones were not viable *in vivo*.

This finding that the intertypic clones between genotypes 1a and 2a were not viable was surprising since flavivirus chimeras containing the structural region of dengue virus type 1 or 2 or of tick-borne encephalitis virus and the nonstructural region of an infectious dengue type 4 virus were viable (Bray and Lai, 1991; Pletnev *et al.*, 1992, 1993). While considerable sequence variation exists between the infectious genotype 1a and 2a clones of HCV (Table 3), these viruses exhibit a higher degree of genetic heterogeneity than do the major genotypes of HCV. For other flaviviruses, however, it was possible to obtain

infectious chimeric clones only if the capsid region was derived from the backbone cDNA clone (Chambers *et al.*, 1999; Pletnev and Men, 1998).

TABLE 3

Percent difference of the amino acid sequences between the infectious clone of genotype 1a (pCV-H77C; Yanagi *et al.*, 1997) and the infectious clone of genotype 2a (pJ6CF) of hepatitis C virus

Genome Region[a]	% difference
Polyprotein	27.9 (839/3007)[b]
Core	8.9 (17/191)
E1	37.0 (71/192)
HVR1	59.3 (16/27)
$E2-_{HVR1}$	27.1 (91/336)
p7	38.1 (24/63)
NS2	41.9 (91/217)
NS3	19.2 (121/631)
NS4A	33.3 (18/54)
NS4B	26.8 (70/261)
NS5A	38.5 (171/444)
NS5B	25.2 (149/591)

a Genome regions defined as in Table 1.
b The numbers in parenthesis indicate the amino acid differences for each region.
Positions with deletions or insertions in E2 (4 aa positions) and NS5A (26 aa positions) were not considered.

Trivial explanations may account for the lack of viability of these intertypic chimeras. First, the two silent mutations introduced in the genotype 1a backbone (one in p7 and one in NS5B) for cloning purposes could potentially eliminate infectivity. This is, however, very unlikely since mutations at these positions exist among field isolates of HCV including strain HC-$J6_{CH}$ (Bukh *et al.*, 1998). Also, it is noteworthy that the three previously published infectious clones of strain H77 had numerous silent nucleotide differences (Hong *et al.*, 1999; Kolykhalov *et al.*, 1997; Yanagi *et al.*, 1997). Second, signal peptidases might not cleave the chimeric E2/p7 or p7/NS2

junction. This seems unlikely, however, since eukaryotic signal peptidases typically recognize the amino acid sequences upstream of the cleavage site [the (-3, -1) rule] (Nielsen *et al.*, 1997) and the amino acids at these two sites are conserved between genotypes 1a and 2a (Fig. 5B). Finally, the E2/p7 and/or p7/NS2 gene junctions could differ between genotypes 1a and 2a. The junctions determined for genotypes 1a and 1b were used (Lin *et al.*, 1994; Mizushima *et al.*, 1994; Selby *et al.*, 1994) because those for genotype 2a have not been identified. In the latter two cases, further analyses of genotype 2a should eventually provide sufficient data to overcome such potential problems and it would most likely be possible to construct a viable chimera.

More complicated explanations for the lack of viability of the chimeras might be required if critical genotype-specific interactions occur as regards the structural proteins, the nonstructural proteins and the genomic RNA. For instance, one cannot rule out that the chimeras were not viable because the IRES function was compromised. In *in vitro* studies the IRES activity depended on RNA sequences not only in the 5' UTR but also extending 3' of the translation initiation site (Hahm *et al.*, 1998; Lemon and Honda, 1997; Reynolds *et al.*, 1995). Although the 3' border of the HCV IRES is still controversial it is believed to involve at most the first 39 nts of the core gene (Lemon and Honda, 1997). The 5' UTR of the intertypic chimeras was either a chimera of genotype 1a and 2a sequences or the entire 5' UTR was derived from the 1a clone (Figs. 4, 5A). Importantly, the 5' end of core is conserved among genotypes 1a and 2a (Fig. 5A). Thus, the predicted

IRES-like secondary structure is maintained in these chimeras, suggesting that the IRES activity most likely was maintained.

Possible interactions between the structural proteins and the nonstructural proteins and/or the genomic RNA, which involve RNA packaging, replication or translation are conceivable. In poliovirus, which is another positive-sense RNA virus, functional coupling of RNA packaging to RNA replication and of RNA replication to translation have been suggested (Novak and Kirkegaard, 1994 ; Nugent *et al.*, 1999). Similar to other viruses of the *Flaviviridae* family, a membrane-associated replicase complex is thought to initiate replication at the 3' end of HCV and to synthesize a complementary negative-strand RNA (Rice, 1996). The putative cis-acting elements at the 5' and 3' termini which are believed to be important for viral genome replication (Rice 1996; Frolov et al., 1998) should be maintained in the intertypic HCV chimeras at least in the two constructs with the authentic 1a 5'UTR. However, it is conceivable that the viral packaging system was interrupted (Frolov *et al.*, 1998). Studies using a Kunjin flavivirus replicon system and providing the structural proteins *in trans* suggested that the essential encapsidation signals did not reside in the structural region of the genome (Khromykh *et al.*, 1997, 1998). The location of the packaging signals of HCV is not known. However, if the structural proteins encapsidate viral RNA via genotype-specific sequences outside of the structural region, the chimeras would be unable to package the RNA and it might be extremely

difficult to construct viable chimeras between highly divergent strains.

Example 3

A consensus molecular clone of genotype 2a is infectious *in vivo*

In order to prove that the genotype 2a portion used in the 4 intertypic chimeric cDNA clones indeed represented the infectious sequence, a consensus full-length cDNA clone of HC-J6$_{CH}$ (pJ6CF) was constructed. The core sequence of the T7 promoter, a 5' guanosine residue and the full-length sequence of HC-J6$_{CH}$ (9711 nts) were cloned into pGEM-9Zf vector using NotI/XbaI sites. Within the HCV sequence there were no deduced amino acid differences and only 4 nucleotide differences (at nucleotide positions 1822, 5494, 9247 and 9289) from the consensus sequence of HC-J6$_{CH}$ as determined in the present study. The silent mutation at position 1822 was within the structural region and so was also present in the four intertypic chimeras. The 5' terminal 16 nts and the 3' terminal 82 nts were deduced from previously published HCV genotype 2a sequences (Okamoto *et al.*, 1991, Tanaka *et al.*, 1996). The full-length cDNA clone of genotype 2a contained a 5' UTR of 340 nts, an ORF of 9099 nts encoding 3033 amino acids and a 3' UTR consisting of a variable region of 39 nts followed by a 132 nucleotide-long polypyrimidine tract interrupted with 3 A residues and the 3' terminal conserved region of 98 nts.

RNA transcripts from pJ6CF were injected into the same chimpanzee used for injection of the 4 intertypic chimeras. The chimpanzee became infected at

the first attempt with an HCV titer of 10^2 GE/ml at week 1 post inoculation (p.i.), and 10^3-10^4 GE/ml during weeks 2 to 6 p.i. The consensus sequence of PCR products of the complete ORF, amplified from serum obtained during week 5 p.i., was identical to the sequence of pJ6CF and there was no evidence of a quasispecies. Since RNA transcripts of this infectious genotype 2a clone were infectious *in vivo*, and it shared an exact sequence with the non-infectious intertypic chimeric clones, their failure to replicate must have been the result of incompatibilities between the genotype 1a and 2a sequences.

To confirm that the chimpanzee used was susceptible also to infection by genotype 1a, which comprised most of the intertypic chimeras, the chimpanzee was subsequently inoculated with RNA transcripts from the infectious genotype 1a clone (pCV-H77C). Serum samples were tested in an H77-specific RT-PCR assay to identify super-infection with genotype 1a. At week 1 p.i. the total HCV genome titer was 10^4 GE/ml and the H77-specific (1a) genome titer was 10^2 GE/ml. The H77-specific genome titer increased to 10^3 GE/ml at week 2 p.i., and reached 10^4 GE/ml during weeks 3-6 p.i. The consensus sequence of PCR products amplified with H77-specific primers at weeks 1-6 p.i. were found to be identical to that of pCV-H77C. However, the direct sequences of PCR products amplified with the 5' UTR primers at weeks 1-2 after inoculation of pCV-H77C were identical to that of pJ6CF indicating that the 2a genotype was still present and represented the majority species. These experiments confirmed that the inability of the intertypic 1a, 2a

cDNA clones to infect the chimpanzee was not the result of protective immune responses in the chimpanzee but represented deficiencies intrinsic to the chimeras.

Discussion

The published infectious cDNA clones of HCV represent the two most important subtypes of genotype 1 (Hong *et al.*, 1999; Kolykhalov *et al.*, 1997; Yanagi *et al.*, 1997, 1998). However, 5 more major genotypes of HCV are recognized. In the above Examples, the infectivity of a cDNA clone of a second major HCV genotype was demonstrated. As in previous studies, the infectivity of RNA transcripts was demonstrated *in vivo* by intrahepatic transfection of a chimpanzee. This new infectious clone (pJ6CF) encodes the consensus polyprotein of HCV strain HC-J6$_{CH}$, genotype 2a. Its encoded polyprotein differs from those of the infectious clones of genotypes 1a and 1b by approximately 30% (Table 2). Genotype 2 strains, in particular subtypes 2a and 2b, have a worldwide distribution and important differences between genotypes 1 and 2 with respect to pathogenesis and treatment were indicated in previous studies. The availability of an infectious clone representing a second major genotype of HCV should permit new ways of studying the molecular biology and immunopathology of this important and genetically quite different human pathogen.

The 5' and 3' UTRs of HCV are believed to be critical for viral replication, translation and viral packaging (Rice, 1996). The 5' 203 terminal nucleotides and the 3' 101 terminal nucleotides of the published infectious clones of genotypes 1a and 1b were identical.

However, the sequences of UTRs of the genotype 2a clone differ from those of the genotype 1 clones. Overall, the 5' UTR of the genotype 2a clone has 17 nt differences and a single nucleotide deletion compared with the infectious clones of genotype 1a (Fig. 5A). Five of these differences and the deletion are within the first 30 nucleotides, whereas the remainder are found within the predicted IRES structure. Differences also exist between the 3' UTR of the genotype 2a clone and the clones of genotype 1a (Fig. 5B). The sequences of the variable region are very different. Recent study has shown this region is not critical for infectivity *in vivo* (Yanagi *et al.*, 1999). Within the regions which are critical for infectivity *in vivo* (Yanagi *et al.*, 1999), the 132 nucleotide-long polypyrimidine tract of the genotype 2a clone has 3 unique A residues interspersed and the 3' terminal conserved region of 98 nts has 4 nt differences within the 3' terminal stable stem-loop structure (Fig. 5B) (Kolykhalov *et al.*, 1996; Tanaka *et al.*, 1996). Since the 2a clone was infectious these sequence differences are apparently real and are compatible with infectivity. Further studies are required to determine whether these represent critical genotype-specific sequences.

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WHAT IS CLAIMED IS:

1. A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, said molecule capable of expressing said virus when transfected into cells.

2. The nucleic acid molecule of claim 1, wherein said molecule encodes the amino acid sequence of SEQ ID NO:2.

3. The nucleic acid molecule of claim 2, wherein said molecule comprises the nucleic acid sequence of SEQ ID NO:1.

4. A DNA construct comprising a nucleic acid molecule according to claim 1.

5. A DNA construct comprising a nucleic acid molecule according to claim 3.

6. An RNA transcript of the DNA construct of claim 4.

7. An RNA transcript of the DNA construct of claim 5.

8. A cell transfected with the DNA construct of claim 4.

9. A cell transfected with the DNA construct of claim 5.

10. A cell transfected with RNA transcript of claim 6.

11. A cell transfected with RNA transcript of claim 7.

12. A hepatitis C virus polypeptide produced by the cell of claims 8 or 9.

13. A hepatitis C virus polypeptide produced by the cell of claims 10 or 11.

14. A hepatitis C virus produced by the cell of claims 8 or 9.

15. A hepatitis C virus produced by the cell of claims 10 or 11.

16. A hepatitis C virus whose genome comprises a nucleic acid molecule according to claim 1.

17. A hepatitis C virus whose genome comprises a nucleic acid molecule according to claim 3.

18. A method for producing a hepatitis C virus comprising transfecting a host cell with the RNA transcript of claims 6 or 7.

19. A polypeptide encoded by a nucleic acid sequence according to claim 1.

20. A polypeptide encoded by a nucleic acid sequence according to claim 3.

21. The polypeptide of claim 19, wherein said polypeptide is selected from the group consisting of NS3 protease, E1 protein, E2 protein or NS4 protein.

22. The polypeptide of claim 20, wherein said polypeptide is selected from the group consisting of NS3 protease, E1 protein, E2 protein or NS4 protein.

23. A method for assaying candidate antiviral agents for activity against HCV, comprising:

a) exposing a cell containing the hepatitis C virus of claims 16 or 17 to the candidate antiviral agent; and

b) measuring the presence or absence of hepatitis C virus replication in the cell of step (a).

24. The method of claim 23, wherein said replication in step (b) is measured by at least one of the following: negative strand RT-PCR, quantitative RT-PCR, Western blot, immunofluoresence, or infectivity in a susceptible animal.

25. A method for assaying candidate antiviral agents for activity against HCV, comprising:

a) exposing an HCV protease encoded by a nucleic acid sequence according to claims 1 or 3 or a fragment thereof to the candidate antiviral agent in the presence of a protease substrate; and

b) measuring the protease activity of said protease.

26. The method of claim 25, wherein said HCV protease is selected from the group consisting of an NS3 domain protease, an NS3-NS4A fusion polypeptide, or an NS2-NS3 protease.

27. An antiviral agent identified as having antiviral activity for HCV by the method of claim 23.

28. An antiviral agent identified as having antiviral activity for HCV by the method of claim 25.

29. Antibody to the polypeptide of claim 19.

30. Antibody to the polypeptide of claim 20.

31. Antibody to the hepatitis C virus of claim 16.

32. Antibody to the hepatitis C virus of claim 17.

33. A method for determining the susceptibility of cells *in vitro* to support HCV infection, comprising the steps of:

a) growing animal cells in vitro;
b) transfecting into said cells the nucleic acid of claim 1; and
c) determining if said cells show indicia of HCV replication.

34. The method according to claim 33, wherein said cells are human cells.

35. A composition comprising a polypeptide of claim 19 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

36. A composition comprising a polypeptide of claim 20 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

37. A composition comprising a nucleic acid molecule of claim 1 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

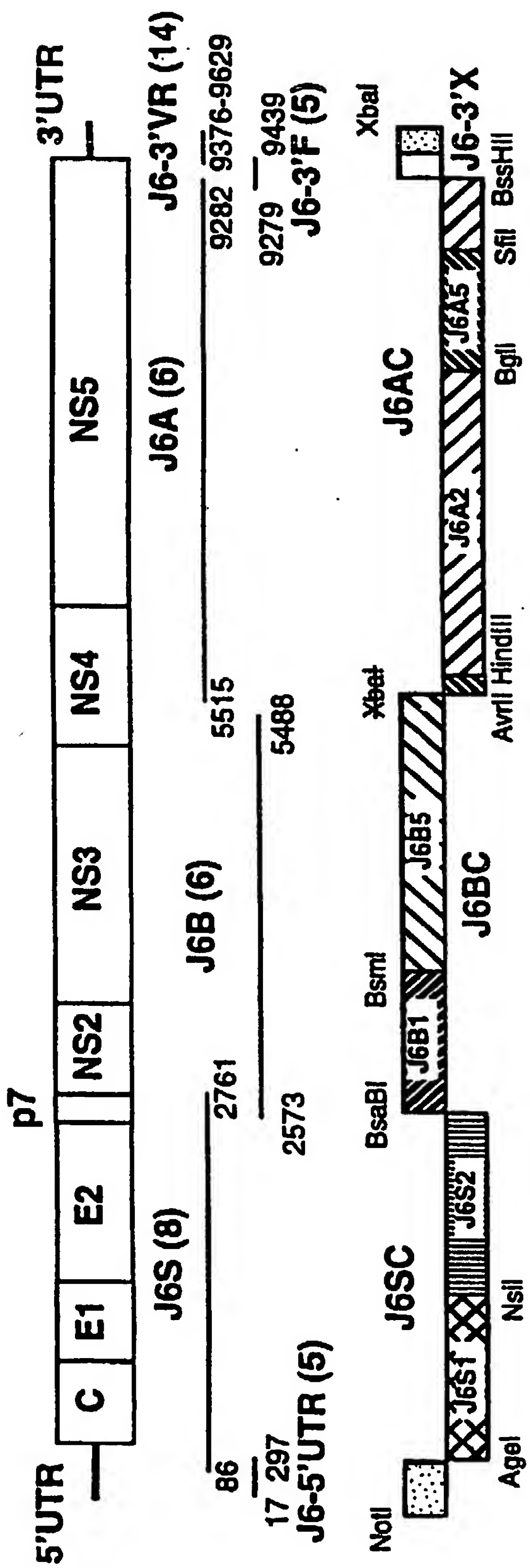

5'UTR
C
E1
E2
p7
NS2
NS3
NS4
NS5
3'UTR
J6S (8)
86
2761
J6-5'UTR (5)
17 297
J6B (6)
2573
5488
J6A (6)
5515
9282
J6-3'VR (14)
9376-9629
J6-3'F (5)
9279
9439
J6SC
J6S1
J6S2
NotI
AgeI
NsiI
BsaBI
J6BC
J6B1
J6B5
BsmI
XbaI
AvrII
HindIII
J6AC
J6A2
J6A5
BglI
SfiI
BssHII
J6-3'X

FIG. 1

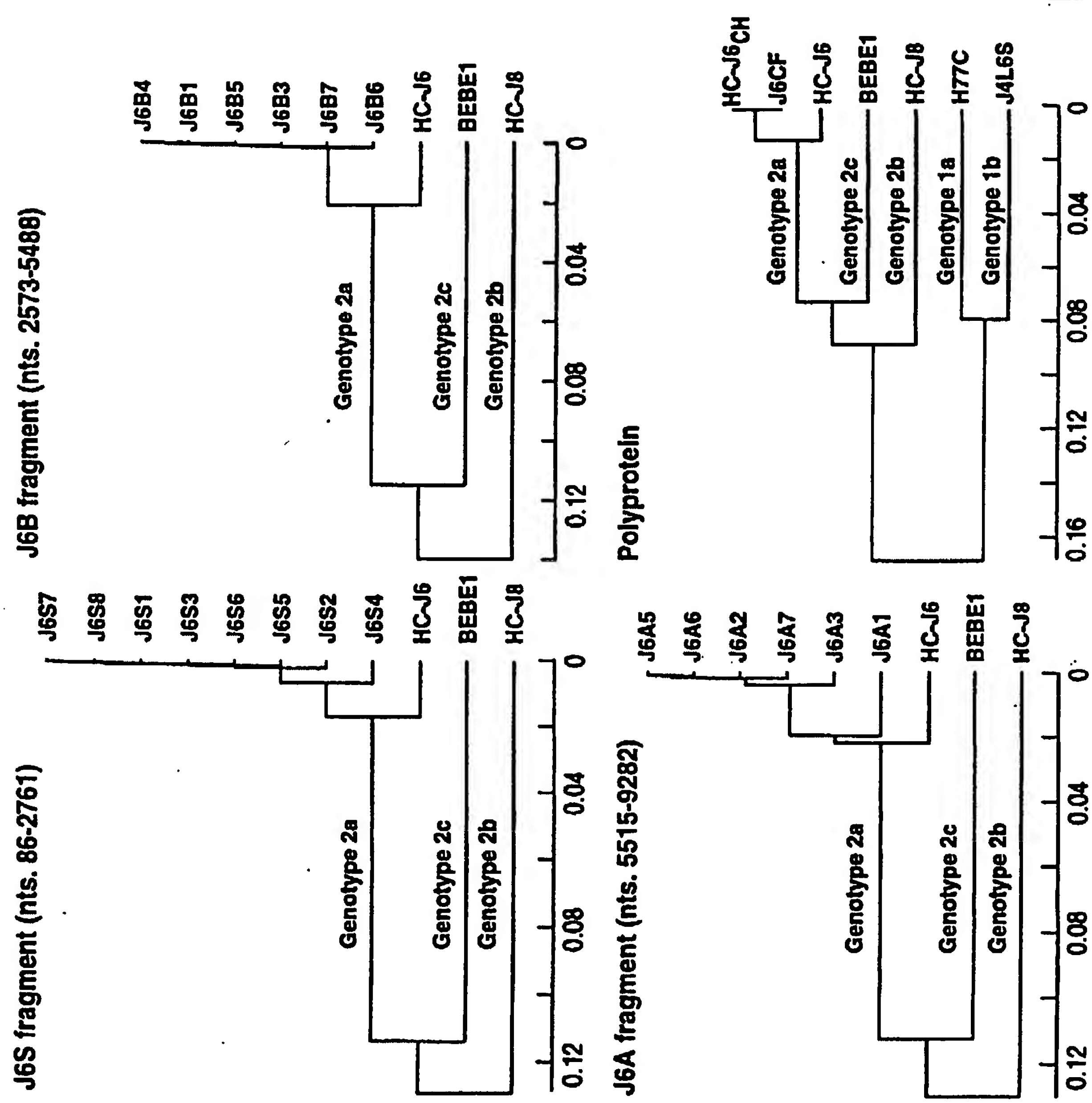

J6S fragment (nts. 86-2761)
J6S7
J6S8
J6S1
J6S3
J6S6
J6S5
J6S2
J6S4
HC-J6
BEBE1
HC-J8
Genotype 2a
Genotype 2c
Genotype 2b
0
0.04
0.08
0.12
J6B fragment (nts. 2573-5488)
J6B4
J6B1
J6B5
J6B3
J6B7
J6B6
HC-J6
BEBE1
HC-J8
Genotype 2a
Genotype 2c
Genotype 2b
0
0.04
0.08
0.12
J6A fragment (nts. 5515-9282)
J6A5
J6A6
J6A2
J6A7
J6A3
J6A1
HC-J6
BEBE1
HC-J8
Genotype 2a
Genotype 2c
Genotype 2b
0
0.04
0.08
0.12
Polyprotein
HC-J6CH
J6CF
HC-J6
BEBE1
HC-J8
H77C
J4L6S
Genotype 2a
Genotype 2c
Genotype 2b
Genotype 1a
Genotype 1b
0
0.04
0.08
0.12
0.16

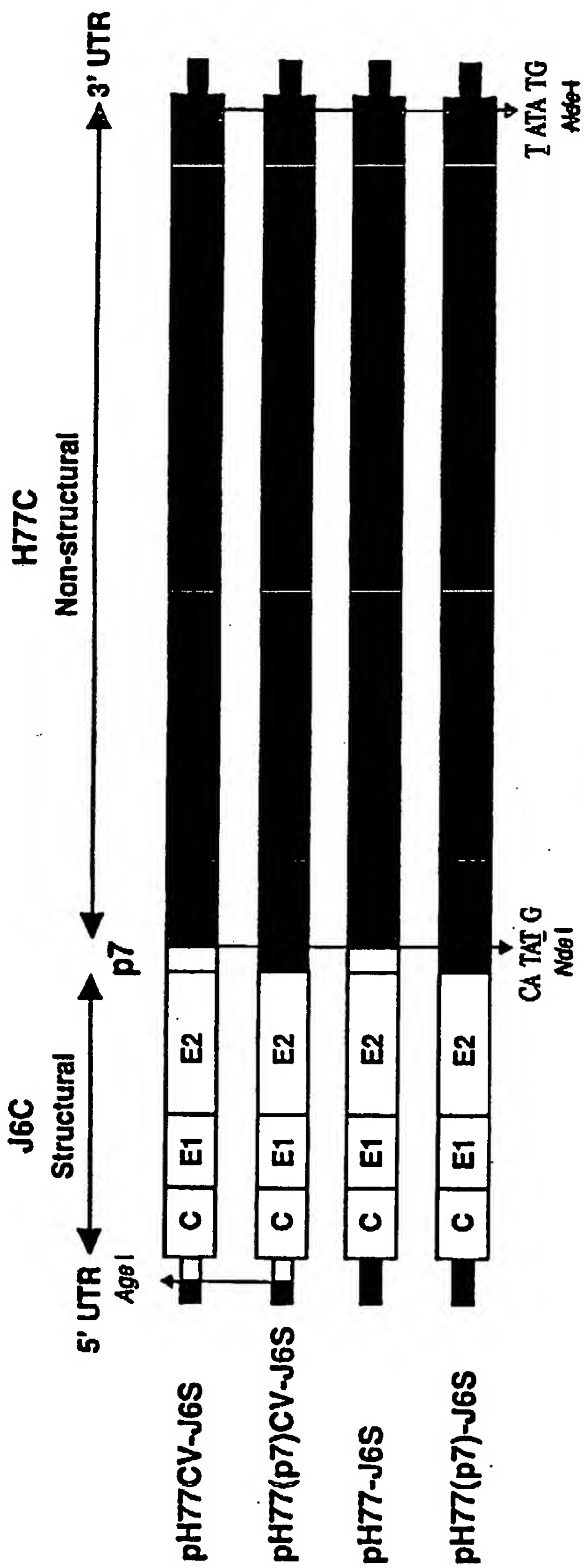
FIG. 2

```
           375                                                     419
HC-J6CH    LLLAAGVDA  RTHTVGGSAAQTTGRLTSLFDMGPRQK  IQLVNTNGS

J6S1       .........  ...........................  .........
J6S2       .........  ...........................  .........
J6S3       .........  ...........................  .........
J6S5       .........  ...........................  .........
J6S6       .........  ...........................  .........
J6S7       .........  ...........................  .........
J6S8       .........  ...........................  .........
J6S4       .........  Q..........................  ...I.....

HC-J6      .........  Q.......T.HNART..GM.SL.A...  ...I.....
                      <------------------------->
                                 HVR1
```

FIG. 3



J6C
Structural
H77C
Non-structural
5' UTR
Age I
p7
3' UTR
C
E1
E2
CA TAT G
Nde I
T ATA TG
Nde I
pH77CV-J6S
pH77(p7)CV-J6S
pH77-J6S
pH77(p7)-J6S

FIG. 4

5' Untranslated Region

FIG. 5A

```
                  1                                                                                                  90
H77C              GCCAGCCCCC TGATGGGGGC GACACTCCAC CATGAATCAC TCCCCTGTGA GGAACTACTG TCTTCACGCA GAAAGCGTCT AGCCATGGCG
H77CV-J6S         .......... .......... .......... .......... .......... .......... .......... .......... ..........
H77(p7)CV-J6S     .......... .......... .......... .......... .......... .......... .......... .......... ..........
H77-J6S           .......... .......... .......... .......... .......... .......... .......... .......... ..........
H77(p7)-J6S       .......... .......... .......... .......... .......... .......... .......... .......... ..........
J6CF              A..C.....- .A..A..... ........G. .......... .......... .......... .......... .......... ..........

                  91                                                                                                 180
H77C              TTAGTATGAG TGTCGTGCAG CCTCCAGGAC CCCCCCTCCC GGGAGAGCCA TAGTGGTCTG CGGAACCGGT GAGTACACCG GAATTGCCAG
H77CV-J6S         .......... .......... .......... .......... .......... .......... .......... .......... ........G.
H77(p7)CV-J6S     .......... .......... .......... .......... .......... .......... .......... .......... ........G.
H77-J6S           .......... .......... .......... .......... .......... .......... .......... .......... ..........
H77(p7)-J6S       .......... .......... .......... .......... .......... .......... .......... .......... ..........
J6CF              .......... ......A... ........C. .......... .......... .......... .......... .......... ........G.
                                                                                        AgeI
                  181                                                                                                270
H77C              GACGACCGGG TCCTTTCTTG GATAAACCCG CTCAATGCCT GGAGATTTGG GCGTGCCCCC GCAAGACTGC TAGCCGAGTA GTGTTGGGTC
H77CV-J6S         ..A...T... .......... .........G ...T.....C ..CC...... .......... .......... .......... .C.......T
H77(p7)CV-J6S     ..A...T... .......... .........G ...T.....C ..CC...... .......... .......... .......... .C.......T
H77-J6S           .......... .......... .......... .......... .......... .......... .......... .......... ..........
H77(p7)-J6S       .......... .......... .......... .......... .......... .......... .......... .......... ..........
J6CF              ..A...T... .......... .........G ...T.....C ..CC...... .......... .......... .......... .C.......T

                  271                                                                                                360
H77C              GCGAAAGGCC TTGTGGTACT GCCTGATAGG GTGCTTGCGA GTGCCCCGGG AGGTCTCGTA GACCGTGCAC CATGAGCACG AATCCTAAAC
H77CV-J6S         .......... .......... .......... .......... .......... .......... .......... .........A ..........
H77(p7)CV-J6S     .......... .......... .......... .......... .......... .......... .......... .........A ..........
H77-J6S           .......... .......... .......... .......... .......... .......... .......... .........A ..........
H77(p7)-J6S       .......... .......... .......... .......... .......... .......... .......... .........A ..........
J6CF              .......... .......... .......... .......... .......... .......... .......... .........A ..........
```

FIG. 5B

3' Untranslated Region

```
                9375                                                                                  9518
H77C            TGAAGGTTGG GGTAAACACT CCGGCCTCTT AAGCCATTTC CTG (Polypyrimidine tract)81  AATGGTGGCT CCATCTTAGC
H77CV-J6S       .......... .......... .......... .......... ... (Polypyrimidine tract)81  .......... ..........
H77(p7)CV-J6S   .......... .......... .......... .......... ... (Polypyrimidine tract)81  .......... ..........
H77-J6S         .......... .......... .......... .......... ... (Polypyrimidine tract)81  .......... ..........
H77(p7)-J6S     .......... .......... .......... .......... ... (Polypyrimidine tract)81  .......... ..........
J6CF            .AG..CGGCA CAC.TTAG.. A.ACT.CA.A GCTAAC.G.. .C- (Polypyrimidine tract)132 ---....... ..........

                9519                                                                          9599
H77C            CCTAGTCACG GCTAGCTGTG AAAGGTCCGT GAGCCGCATG ACTGCAGAGA GTGCTGATAC TGGCCTCTCT GCAGATCATG T
H77CV-J6S       .......... .......... .......... .......... .......... .......... .......... .......... .
H77(p7)CV-J6S   .......... .......... .......... .......... .......... .......... .......... .......... .
H77-J6S         .......... .......... .......... .......... .......... .......... .......... .......... .
H77(p7)-J6S     .......... .......... .......... .......... .......... .......... .......... .......... .
J6CF            .......... .......... .......... .......... .......... ....C.TA.. ...T...... .......... .
```

E2/p7/NS2 Region

```
                                E2/p7                                                             p7/NS2
                                  ↓                      p7                                         ↓
                730                                                                                                825
H77C            RVCSCLWMMLLISQAEA ALENLVILNAASLAGTHGLVSFLVFFCFAWYLKGRWVPGAVYALYGMWPLLLLLLALPQRAYA LDTEVAASCGGVVLVG
H77CV-J6S       ...A....LI.LG.... ...K....H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS........Q... ................
H77(p7)CV-J6S   ...A....LI.LG.... ................................................................ ................
H77-J6S         ...A....LI.LG.... ...K....H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS........Q... ................
H77(p7)-J6S     ...A....LI.LG.... ................................................................ ................
J6CF            ...A....LI.LG.... ...K....H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS........Q... Y.AS.HGQI.AAL..M
```

H77C

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATAAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCAAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GTCGCCCACA	400
GGACGTCAAG	TTCCCGGGTG	GCGGTCAGAT	CGTTGGTGGA	GTTTACTTGT	450
TGCCGCGCAG	GGGCCCTAGA	TTGGGTGTGC	GCGCGACGAG	GAAGACTTCC	500
GAGCGGTCGC	AACCTCGAGG	TAGACGTCAG	CCTATCCCCA	AGGCACGTCG	550
GCCCGAGGGC	AGGACCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	TTGCGGGTGG	GCGGGATGGC	TCCTGTCTCC	CCGTGGCTCT	650
CGGCCTAGCT	GGGGCCCCAC	AGACCCCCGG	CGTAGGTCGC	GCAATTTGGG	700
TAAGGTCATC	GATACCCTTA	CGTGCGGCTT	CGCCGACCTC	ATGGGGTACA	750
TACCGCTCGT	CGGCGCCCCT	CTTGGAGGCG	CTGCCAGGGC	CCTGGCGCAT	800
GGCGTCCGGG	TTCTGGAAGA	CGGCGTGAAC	TATGCAACAG	GGAACCTTCC	850
TGGTTGCTCT	TTCTCTATCT	TCCTTCTGGC	CCTGCTCTCT	TGCCTGACTG	900
TGCCCGCTTC	AGCCTACCAA	GTGCGCAATT	CCTCGGGGCT	TTACCATGTC	950
ACCAATGATT	GCCCTAACTC	GAGTATTGTG	TACGAGGCGG	CCGATGCCAT	1000
CCTGCACACT	CCGGGGTGTG	TCCCTTGCGT	TCGCGAGGGT	AACGCCTCGA	1050
GGTGTTGGGT	GGCGGTGACC	CCCACGGTGG	CCACCAGGGA	CGGCAAACTC	1100
CCCACAACGC	AGCTTCGACG	TCATATCGAT	CTGCTTGTCG	GGAGCGCCAC	1150
CCTCTGCTCG	GCCCTCTACG	TGGGGGACCT	GTGCGGGTCT	GTCTTTCTTG	1200
TTGGTCAACT	GTTTACCTTC	TCTCCCAGGC	GCCACTGGAC	GACGCAAGAC	1250
TGCAATTGTT	CTATCTATCC	CGGCCATATA	ACGGGTCATC	GCATGGCATG	1300
GGATATGATG	ATGAACTGGT	CCCCTACGGC	AGCGTTGGTG	GTAGCTCAGC	1350
TGCTCCGGAT	CCCACAAGCC	ATCATGGACA	TGATCGCTGG	TGCTCACTGG	1400
GGAGTCCTGG	CGGGCATAGC	GTATTTCTCC	ATGGTGGGGA	ACTGGGCGAA	1450
GGTCCTGGTA	GTGCTGCTGC	TATTTGCCGG	CGTCGACGCG	GAAACCCACG	1500
TCACCGGGGG	AAATGCCGGC	CGCACCACGG	CTGGGCTTGT	TGGTCTCCTT	1550
ACACCAGGCG	CCAAGCAGAA	CATCCAACTG	ATCAACACCA	ACGGCAGTTG	1600
GCACATCAAT	AGCACGGCCT	TGAATTGCAA	TGAAAGCCTT	AACACCGGCT	1650
GGTTAGCAGG	GCTCTTCTAT	CAACACAAAT	TCAACTCTTC	AGGCTGTCCT	1700
GAGAGGTTGG	CCAGCTGCCG	ACGCCTTACC	GATTTTGCCC	AGGGCTGGGG	1750
TCCTATCAGT	TATGCCAACG	GAAGCGGCCT	CGACGAACGC	CCCTACTGCT	1800
GGCACTACCC	TCCAAGACCT	TGTGGCATTG	TGCCCGCAAA	GAGCGTGTGT	1850
GGCCCGGTAT	ATTGCTTCAC	TCCCAGCCCC	GTGGTGGTGG	GAACGACCGA	1900

FIG. 6A

H77C

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
CAGGTCGGGC	GCGCCTACCT	ACAGCTGGGG	TGCAAATGAT	ACGGATGTCT	1950
TCGTCCTTAA	CAACACCAGG	CCACCGCTGG	GCAATTGGTT	CGGTTGTACC	2000
TGGATGAACT	CAACTGGATT	CACCAAAGTG	TGCGGAGCGC	CCCCTTGTGT	2050
CATCGGAGGG	GTGGGCAACA	ACACCTTGCT	CTGCCCCACT	GATTGCTTCC	2100
GCAAACATCC	GGAAGCCACA	TACTCTCGGT	GCGGCTCCGG	TCCCTGGATT	2150
ACACCCAGGT	GCATGGTCGA	CTACCCGTAT	AGGCTTTGGC	ACTATCCTTG	2200
TACCATCAAT	TACACCATAT	TCAAAGTCAG	GATGTACGTG	GGAGGGGTCG	2250
AGCACAGGCT	GGAAGCGGCC	TGCAACTGGA	CGCGGGGCGA	ACGCTGTGAT	2300
CTGGAAGACA	GGGACAGGTC	CGAGCTCAGC	CCGTTGCTGC	TGTCCACCAC	2350
ACAGTGGCAG	GTCCTTCCGT	GTTCTTTCAC	GACCCTGCCA	GCCTTGTCCA	2400
CCGGCCTCAT	CCACCTCCAC	CAGAACATTG	TGGACGTGCA	GTACTTGTAC	2450
GGGGTAGGGT	CAAGCATCGC	GTCCTGGGCC	ATTAAGTGGG	AGTACGTCGT	2500
TCTCCTGTTC	CTTCTGCTTG	CAGACGCGCG	CGTCTGCTCC	TGCTTGTGGA	2550
TGATGTTACT	CATATCCCAA	GCGGAGGCGG	CTTTGGAGAA	CCTCGTAATA	2600
CTCAATGCAG	CATCCCTGGC	CGGGACGCAC	GGTCTTGTGT	CCTTCCTCGT	2650
GTTCTTCTGC	TTTGCGTGGT	ATCTGAAGGG	TAGGTGGGTG	CCCGGAGCGG	2700
TCTACGCCCT	CTACGGGATG	TGGCCTCTCC	TCCTGCTCCT	GCTGGCGTTG	2750
CCTCAGCGGG	CATACGCACT	GGACACGGAG	GTGGCCGCGT	CGTGTGGCGG	2800
CGTTGTTCTT	GTCGGGTTAA	TGGCGCTGAC	TCTGTCGCCA	TATTACAAGC	2850
GCTATATCAG	CTGGTGCATG	TGGTGGCTTC	AGTATTTTCT	GACCAGAGTA	2900
GAAGCGCAAC	TGCACGTGTG	GGTTCCCCCC	CTCAACGTCC	GGGGGGGCCG	2950
CGATGCCGTC	ATCTTACTCA	TGTGTGTAGT	ACACCCGACC	CTGGTATTTG	3000
ACATCACCAA	ACTACTCCTG	GCCATCTTCG	GACCCCTTTG	GATTCTTCAA	3050
GCCAGTTTGC	TTAAAGTCCC	CTACTTCGTG	CGCGTTCAAG	GCCTTCTCCG	3100
GATCTGCGCG	CTAGCGCGGA	AGATAGCCGG	AGGTCATTAC	GTGCAAATGG	3150
CCATCATCAA	GTTAGGGGCG	CTTACTGGCA	CCTATGTGTA	TAACCATCTC	3200
ACCCCTCTTC	GAGACTGGGC	GCACAACGGC	CTGCGAGATC	TGGCCGTGGC	3250
TGTGGAACCA	GTCGTCTTCT	CCCGAATGGA	GACCAAGCTC	ATCACGTGGG	3300
GGGCAGATAC	CGCCGCGTGC	GGTGACATCA	TCAACGGCTT	GCCCGTCTCT	3350
GCCCGTAGGG	GCCAGGAGAT	ACTGCTTGGG	CCAGCCGACG	GAATGGTCTC	3400
CAAGGGGTGG	AGGTTGCTGG	CGCCCATCAC	GGCGTACGCC	CAGCAGACGA	3450
GAGGCCTCCT	AGGGTGTATA	ATCACCAGCC	TGACTGGCCG	GGACAAAAAC	3500
CAAGTGGAGG	GTGAGGTCCA	GATCGTGTCA	ACTGCTACCC	AAACCTTCCT	3550
GGCAACGTGC	ATCAATGGGG	TATGCTGGAC	TGTCTACCAC	GGGGCCGGAA	3600
CGAGGACCAT	CGCATCACCC	AAGGGTCCTG	TCATCCAGAT	GTATACCAAT	3650
GTGGACCAAG	ACCTTGTGGG	CTGGCCCGCT	CCTCAAGGTT	CCCGCTCATT	3700
GACACCCTGT	ACCTGCGGCT	CCTCGGACCT	TTACCTGGTC	ACGAGGCACG	3750
CCGATGTCAT	TCCCGTGCGC	CGGCGAGGTG	ATAGCAGGGG	TAGCCTGCTT	3800

FIG. 6B

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGCCCCGGC	CCATTTCCTA	CTTGAAAGGC	TCCTCGGGGG	GTCCGCTGTT	3850
GTGCCCCGCG	GGACACGCCG	TGGGCCTATT	CAGGGCCGCG	GTGTGCACCC	3900
GTGGAGTGGC	TAAAGCGGTG	GACTTTATCC	CTGTGGAGAA	CCTAGGGACA	3950
ACCATGAGAT	CCCCGGTGTT	CACGGACAAC	TCCTCTCCAC	CAGCAGTGCC	4000
CCAGAGCTTC	CAGGTGGCCC	ACCTGCATGC	TCCCACCGGC	AGCGGTAAGA	4050
GCACCAAGGT	CCCGGCTGCG	TACGCAGCCC	AGGGCTACAA	GGTGTTGGTG	4100
CTCAACCCCT	CTGTTGCTGC	AACGCTGGGC	TTTGGTGCTT	ACATGTCCAA	4150
GGCCCATGGG	GTTGATCCTA	ATATCAGGAC	CGGGGTGAGA	ACAATTACCA	4200
CTGGCAGCCC	CATCACGTAC	TCCACCTACG	GCAAGTTCCT	TGCCGACGGC	4250
GGGTGCTCAG	GAGGTGCTTA	TGACATAATA	ATTTGTGACG	AGTGCCACTC	4300
CACGGATGCC	ACATCCATCT	TGGGCATCGG	CACTGTCCTT	GACCAAGCAG	4350
AGACTGCGGG	GGCGAGACTG	GTTGTGCTCG	CCACTGCTAC	CCCTCCGGGC	4400
TCCGTCACTG	TGTCCCATCC	TAACATCGAG	GAGGTTGCTC	TGTCCACCAC	4450
CGGAGAGATC	CCCTTTTACG	GCAAGGCTAT	CCCCCTCGAG	GTGATCAAGG	4500
GGGGAAGACA	TCTCATCTTC	TGCCACTCAA	AGAAGAAGTG	CGACGAGCTC	4550
GCCGCGAAGC	TGGTCGCATT	GGGCATCAAT	GCCGTGGCCT	ACTACCGCGG	4600
TCTTGACGTG	TCTGTCATCC	CGACCAGCGG	CGATGTTGTC	GTCGTGTCGA	4650
CCGATGCTCT	CATGACTGGC	TTTACCGGCG	ACTTCGACTC	TGTGATAGAC	4700
TGCAACACGT	GTGTCACTCA	GACAGTCGAT	TTCAGCCTTG	ACCCTACCTT	4750
TACCATTGAG	ACAACCACGC	TCCCCCAGGA	TGCTGTCTCC	AGGACTCAAC	4800
GCCGGGGCAG	GACTGGCAGG	GGGAAGCCAG	GCATCTATAG	ATTTGTGGCA	4850
CCGGGGGAGC	GCCCCTCCGG	CATGTTCGAC	TCGTCCGTCC	TCTGTGAGTG	4900
CTATGACGCG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCC	GAGACTACAG	4950
TTAGGCTACG	AGCGTACATG	AACACCCCGG	GGCTTCCCGT	GTGCCAGGAC	5000
CATCTTGAAT	TTTGGGAGGG	CGTCTTTACG	GGCCTCACTC	ATATAGATGC	5050
CCACTTTTTA	TCCCAGACAA	AGCAGAGTGG	GGAGAACTTT	CCTTACCTGG	5100
TAGCGTACCA	AGCCACCGTG	TGCGCTAGGG	CTCAAGCCCC	TCCCCCATCG	5150
TGGGACCAGA	TGTGGAAGTG	TTTGATCCGC	CTTAAACCCA	CCCTCCATGG	5200
GCCAACACCC	CTGCTATACA	GACTGGGCGC	TGTTCAGAAT	GAAGTCACCC	5250
TGACGCACCC	AATCACCAAA	TACATCATGA	CATGCATGTC	GGCCGACCTG	5300
GAGGTCGTCA	CGAGCACCTG	GGTGCTCGTT	GGCGGCGTCC	TGGCTGCTCT	5350
GGCCGCGTAT	TGCCTGTCAA	CAGGCTGCGT	GGTCATAGTG	GGCAGGATCG	5400
TCTTGTCCGG	GAAGCCGGCA	ATTATACCTG	ACAGGGAGGT	TCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGCTCTCAG	CACTTACCGT	ACATCGAGCA	5500
AGGGATGATG	CTCGCTGAGC	AGTTCAAGCA	GAAGGCCCTC	GGCCTCCTGC	5550
AGACCGCGTC	CCGCCATGCA	GAGGTTATCA	CCCCTGCTGT	CCAGACCAAC	5600
TGGCAGAAAC	TCGAGGTCTT	TTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
TGGGATACAA	TACTTGGCGG	GCCTGTCAAC	GCTGCCTGGT	AACCCCGCCA	5700

FIG. 6C

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTGCTTCATT	GATGGCTTTT	ACAGCTGCCG	TCACCAGCCC	ACTAACCACT	5750
GGCCAAACCC	TCCTCTTCAA	CATATTGGGG	GGGTGGGTGG	CTGCCCAGCT	5800
CGCCGCCCCC	GGTGCCGCTA	CTGCCTTTGT	GGGTGCTGGC	CTAGCTGGCG	5850
CCGCCATCGG	CAGCGTTGGA	CTGGGGAAGG	TCCTCGTGGA	CATTCTTGCA	5900
GGGTATGGCG	CGGGCGTGGC	GGGAGCTCTT	GTAGCATTCA	AGATCATGAG	5950
CGGTGAGGTC	CCCTCCACGG	AGGACCTGGT	CAATCTGCTG	CCCGCCATCC	6000
TCTCGCCTGG	AGCCCTTGTA	GTCGGTGTGG	TCTGCGCAGC	AATACTGCGC	6050
CGGCACGTTG	GCCCGGGCGA	GGGGGCAGTG	CAATGGATGA	ACCGGCTAAT	6100
AGCCTTCGCC	TCCCGGGGGA	ACCATGTTTC	CCCCACGCAC	TACGTGCCGG	6150
AGAGCGATGC	AGCCGCCCGC	GTCACTGCCA	TACTCAGCAG	CCTCACTGTA	6200
ACCCAGCTCC	TGAGGCGACT	GCATCAGTGG	ATAAGCTCGG	AGTGTACCAC	6250
TCCATGCTCC	GGTTCCTGGC	TAAGGGACAT	CTGGGACTGG	ATATGCGAGG	6300
TGCTGAGCGA	CTTTAAGACC	TGGCTGAAAG	CCAAGCTCAT	GCCACAACTG	6350
CCTGGGATTC	CCTTTGTGTC	CTGCCAGCGC	GGGTATAGGG	GGGTCTGGCG	6400
AGGAGACGGC	ATTATGCACA	CTCGCTGCCA	CTGTGGAGCT	GAGATCACTG	6900
GACATGTCAA	AAACGGGACG	ATGAGGATCG	TCGGTCCTAG	GACCTGCAGG	6950
AACATGTGGA	GTGGGACGTT	CCCCATTAAC	GCCTACACCA	CGGGCCCCTG	6550
TACTCCCCTT	CCTGCGCCGA	ACTATAAGTT	CGCGCTGTGG	AGGGTGTCTG	6600
CAGAGGAATA	CGTGGAGATA	AGGCGGGTGG	GGGACTTCCA	CTACGTATCG	6650
GGTATGACTA	CTGACAATCT	TAAATGCCCG	TGCCAGATCC	CATCGCCCGA	6700
ATTTTTCACA	GAATTGGACG	GGGTGCGCCT	ACACAGGTTT	GCGCCCCCTT	6750
GCAAGCCCTT	GCTGCGGGAG	GAGGTATCAT	TCAGAGTAGG	ACTCCACGAG	6800
TACCCGGTGG	GGTCGCAATT	ACCTTGCGAG	CCCGAACCGG	ACGTAGCCGT	6850
GTTGACGTCC	ATGCTCACTG	ATCCCTCCCA	TATAACAGCA	GAGGCGGCCG	6900
GGAGAAGGTT	GGCGAGAGGG	TCACCCCCTT	CTATGGCCAG	CTCCTCGGCT	6950
AGCCAGCTGT	CCGCTCCATC	TCTCAAGGCA	ACTTGCACCG	CCAACCATGA	7000
CTCCCCTGAC	GCCGAGCTCA	TAGAGGCTAA	CCTCCTGTGG	AGGCAGGAGA	7050
TGGGCGGCAA	CATCACCAGG	GTTGAGTCAG	AGAACAAAGT	GGTGATTCTG	7100
GACTCCTTCG	ATCCGCTTGT	GGCAGAGGAG	GATGAGCGGG	AGGTCTCCGT	7150
ACCTGCAGAA	ATTCTGCGGA	AGTCTCGGAG	ATTCGCCCGG	GCCCTGCCCG	7200
TCTGGGCGCG	GCCGGACTAC	AACCCCCCGC	TAGTAGAGAC	GTGGAAAAAG	7250
CCTGACTACG	AACCACCTGT	GGTCCATGGC	TGCCCGCTAC	CACCTCCACG	7300
GTCCCCTCCT	GTGCCTCCGC	CTCGGAAAAA	GCGTACGGTG	GTCCTCACCG	7350
AATCAACCCT	ATCTACTGCC	TTGGCCGAGC	TTGCCACCAA	AAGTTTTGGC	7400
AGCTCCTCAA	CTTCCGGCAT	TACGGGCGAC	AATACGACAA	CATCCTCTGA	7450
GCCCGCCCCT	TCTGGCTGCC	CCCCCGACTC	CGACGTTGAG	TCCTATTCTT	7500
CCATGCCCCC	CCTGGAGGGG	GAGCCTGGGG	ATCCGGATCT	CAGCGACGGG	7550
TCATGGTCGA	CGGTCAGTAG	TGGGGCCGAC	ACGGAAGATG	TCGTGTGCTG	7600

FIG. 6D

H77C

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
CTCAATGTCT	TATTCCTGGA	CAGGCGCACT	CGTCACCCCG	TGCGCTGCGG	7650
AAGAACAAAA	ACTGCCCATC	AACGCACTGA	GCAACTCGTT	GCTACGCCAT	7700
CACAATCTGG	TGTATTCCAC	CACTTCACGC	AGTGCTTGCC	AAAGGCAGAA	7750
GAAAGTCACA	TTTGACAGAC	TGCAAGTTCT	GGACAGCCAT	TACCAGGACG	7800
TGCTCAAGGA	GGTCAAAGCA	GCGGCGTCAA	AAGTGAAGGC	TAACTTGCTA	7850
TCCGTAGAGG	AAGCTTGCAG	CCTGACGCCC	CCACATTCAG	CCAAATCCAA	7900
GTTTGGCTAT	GGGGCAAAAG	ACGTCCGTTG	CCATCCCAGA	AAGGCCGTAG	7950
CCCACATCAA	CTCCGTGTGG	AAAGACCTTC	TGGAAGACAG	TGTAACACCA	8000
ATAGACACTA	CCATCATGGC	CAAGAACGAG	GTTTTCTGCG	TTCAGCCTGA	8050
GAAGGGGGGT	CGTAAGCCAG	CTCGTCTCAT	CGTGTTCCCC	GACCTGGGCG	8100
TGCGCGTGTG	CGAGAAGATG	GCCCTGTACG	ACGTGGTTAG	CAAGCTCCCC	8150
CTGGCCGTGA	TGGGAAGCTC	CTACGGATTC	CAATACTCAC	CAGGACAGCG	8200
GGTTGAATTC	CTCGTGCAAG	CGTGGAAGTC	CAAGAAGACC	CCGATGGGGT	8250
TCTCGTATGA	TACCCGCTGT	TTTGACTCCA	CAGTCACTGA	GAGCGACATC	8300
CGTACGGAGG	AGGCAATTTA	CCAATGTTGT	GACCTGGACC	CCCAAGCCCG	8350
CGTGGCCATC	AAGTCCCTCA	CTGAGAGGCT	TTATGTTGGG	GGCCCTCTTA	8400
CCAATTCAAG	GGGGGAAAAC	TGCGGCTACC	GCAGGTGCCG	CGCGAGCGGC	8450
GTACTGACAA	CTAGCTGTGG	TAACACCCTC	ACTTGCTACA	TCAAGGCCCG	8500
GGCAGCCTGT	CGAGCCGCAG	GGCTCCAGGA	CTGCACCATG	CTCGTGTGTG	8550
GCGACGACTT	AGTCGTTATC	TGTGAAAGTG	CGGGGGTCCA	GGAGGACGCG	8600
GCGAGCCTGA	GAGCCTTCAC	GGAGGCTATG	ACCAGGTACT	CCGCCCCCCC	8650
CGGGGACCCC	CCACAACCAG	AATACGACTT	GGAGCTTATA	ACATCATGCT	8700
CCTCCAACGT	GTCAGTCGCC	CACGACGGCG	CTGGAAAGAG	GGTCTACTAC	8750
CTTACCCGTG	ACCCTACAAC	CCCCCTCGCG	AGAGCCGCGT	GGGAGACAGC	8800
AAGACACACT	CCAGTCAATT	CCTGGCTAGG	CAACATAATC	ATGTTTGCCC	8850
CCACACTGTG	GGCGAGGATG	ATACTGATGA	CCCATTTCTT	TAGCGTCCTC	8900
ATAGCCAGGG	ATCAGCTTGA	ACAGGCTCTT	AACTGTGAGA	TCTACGGAGC	8950
CTGCTACTCC	ATAGAACCAC	TGGATCTACC	TCCAATCATT	CAAAGACTCC	9000
ATGGCCTCAG	CGCATTTTCA	CTCCACAGTT	ACTCTCCAGG	TGAAATCAAT	9050
AGGGTGGCCG	CATGCCTCAG	AAAACTTGGG	GTCCCGCCCT	TGCGAGCTTG	9100
GAGACACCGG	GCCCGGAGCG	TCCGCGCTAG	GCTTCTGTCC	AGAGGAGGCA	9150
GGCTGCCCAT	ATGTGGCAAG	TACCTCTTCA	ACTGGGCAGT	AAGAACAAAG	9200
CTCAAACTCA	CTCCAATAGC	GGCCGCTGGC	CGGCTGGACT	TGTCCGGTTG	9250
GTTCACGGCT	GGCTACAGCG	GGGGAGACAT	TTATCACAGC	GTGTCTCATG	9300
CCCGGCCCCG	CTGGTTCTGG	TTTTGCCTAC	TCCTGCTCGC	TGCAGGGGTA	9350
GGCATCTACC	TCCTCCCCAA	CCGATGAAGG	TTGGGGTAAA	CACTCCGGCC	9400
TCTTAAGCCA	TTTCCTGTTT	TTTTTTTTTT	TTTTTTTTTT	TTTTTCTTTT	9450
TTTTTTTCTT	TCCTTTCCTT	CTTTTTTTCC	TTTCTTTTTC	CCTTCTTTAA	9500

FIG. 6E

H77C

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGGTGGCTCC ATCTTAGCCC TAGTCACGGC TAGCTGTGAA AGGTCCGTGA   9550
GCCGCATGAC TGCAGAGAGT GCTGATACTG GCCTCTCTGC AGATCATGT    9599
```

FIG. 6F

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSTNPKPQRK	TKRNTNRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KTSERSQPRG	RRQPIPKARR	PEGRTWAQPG	YPWPLYGNEG	CGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTVPAS	AYQVRNSSGL	200
YHVTNDCPNS	SIVYEAADAI	LHTPGCVPCV	REGNASRCWV	AVTPTVATRD	250
GKLPTTQLRR	HIDLLVGSAT	LCSALYVGDL	CGSVFLVGQL	FTFSPRRHWT	300
TQDCNCSIYP	GHITGHRMAW	DMMMNWSPTA	ALVVAQLLRI	PQAIMDMIAG	350
AHWGVLAGIA	YFSMVGNWAK	VLVVLLLFAG	VDAETHVTGG	NAGRTTAGLV	400
GLLTPGAKQN	IQLINTNGSW	HINSTALNCN	ESLNTGWLAG	LFYQHKFNSS	450
GCPERLASCR	RLTDFAQGWG	PISYANGSGL	DERPYCWHYP	PRPCGIVPAK	500
SVCGPVYCFT	PSPVVVGTTD	RSGAPTYSWG	ANDTDVFVLN	NTRPPLGNWF	550
GCTWMNSTGF	TKVCGAPPCV	IGGVGNNTLL	CPTDCFRKHP	EATYSRCGSG	600
PWITPRCMVD	YPYRLWHYPC	TINYTIFKVR	MYVGGVEHRL	EAACNWTRGE	650
RCDLEDRDRS	ELSPLLLSTT	QWQVLPCSFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSSIA	SWAIKWEYVV	LLFLLLADAR	VCSCLWMMLL	ISQAEAALEN	750
LVILNAASLA	GTHGLVSFLV	FFCFAWYLKG	RWVPGAVYAL	YGMWPLLLLL	800
LALPQRAYAL	DTEVAASCGG	VVLVGLMALT	LSPYYKRYIS	WCMWWLQYFL	850
TRVEAQLHVW	VPPLNVRGGR	DAVILLMCVV	HPTLVFDITK	LLLAIFGPLW	900
ILQASLLKVP	YFVRVQGLLR	ICALARKIAG	GHYVQMAIIK	LGALTGTYVY	950
NHLTPLRDWA	HNGLRDLAVA	VEPVVFSRME	TKLITWGADT	AACGDIINGL	1000
PVSARRGQEI	LLGPADGMVS	KGWRLLAPIT	AYAQQTRGLL	GCIITSLTGR	1050
DKNQVEGEVQ	IVSTATQTFL	ATCINGVCWT	VYHGAGTRTI	ASPKGPVIQM	1100
YTNVDQDLVG	WPAPQGSRSL	TPCTCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPISY	LKGSSGGPLL	CPAGHAVGLF	RAAVCTRGVA	KAVDFIPVEN	1200
LGTTMRSPVF	TDNSSPPAVP	QSFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGVDPNIRT	GVRTITTGSP	ITYSTYGKFL	1300
ADGGCSGGAY	DIIICDECHS	TDATSILGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVSHP	NIEEVALSTT	GEIPFYGKAI	PLEVIKGGRH	LIFCHSKKKC	1400
DELAAKLVAL	GINAVAYYRG	LDVSVIPTSG	DVVVVSTDAL	MTGFTGDFDS	1450
VIDCNTCVTQ	TVDFSLDPTF	TIETTTLPQD	AVSRTQRRGR	TGRGKPGIYR	1500
FVAPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETTVRLR	AYMNTPGLPV	1550
CQDHLEFWEG	VFTGLTHIDA	HFLSQTKQSG	ENFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVTLTHP	ITKYIMTCMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLSTGCV	VIVGRIVLSG	KPAIIPDREV	1700
LYQEFDEMEE	CSQHLPYIEQ	GMMLAEQFKQ	KALGLLQTAS	RHAEVITPAV	1750
QTNWQKLEVF	WAKHMWNFIS	GIQYLAGLST	LPGNPAIASL	MAFTAAVTSP	1800
LTTGQTLLFN	ILGGWVAAQL	AAPGAATAFV	GAGLAGAAIG	SVGLGKVLVD	1850
ILAGYGAGVA	GALVAFKIMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVVCAA	1900

FIG. 6G

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPGE	GAVQWMNRLI	AFASRGNHVS	PTHYVPESDA	AARVTAILSS	1950
LTVTQLLRRL	HQWISSECTT	PCSGSWLRDI	WDWICEVLSD	FKTWLKAKLM	2000
PQLPGIPFVS	CQRGYRGVWR	GDGIMHTRCH	CGAEITGHVK	NGTMRIVGPR	2050
TCRNMWSGTF	PINAYTTGPC	TPLPAPNYKF	ALWRVSAEEY	VEIRRVGDFH	2100
YVSGMTTDNL	KCPCQIPSPE	FFTELDGVRL	HRFAPPCKPL	LREEVSFRVG	2150
LHEYPVGSQL	PCEPEPDVAV	LTSMLTDPSH	ITAEAAGRRL	ARGSPPSMAS	2200
SSASQLSAPS	LKATCTANHD	SPDAELIEAN	LLWRQEMGGN	ITRVESENKV	2250
VILDSFDPLV	AEEDEREVSV	PAEILRKSRR	FARALPVWAR	PDYNPPLVET	2300
WKKPDYEPPV	VHGCPLPPPR	SPPVPPPRKK	RTVVLTESTL	STALAELATK	2350
SFGSSSTSGI	TGDNTTTSSE	PAPSGCPPDS	DVESYSSMPP	LEGEPGDPDL	2400
SDGSWSTVSS	GADTEDVVCC	SMSYSWTGAL	VTPCAAEEQK	LPINALSNSL	2450
LRHHNLVYST	TSRSACQRQK	KVTFDRLQVL	DSHYQDVLKE	VKAAASKVKA	2500
NLLSVEEACS	LTPPHSAKSK	FGYGAKDVRC	HARKAVAHIN	SVWKDLLEDS	2550
VTPIDTTIMA	KNEVFCVQPE	KGGRKPARLI	VFPDLGVRVC	EKMALYDVVS	2600
KLPLAVMGSS	YGFQYSPGQR	VEFLVQAWKS	KKTPMGFSYD	TRCFDSTVTE	2650
SDIRTEEAIY	QCCDLDPQAR	VAIKSLTERL	YVGGPLTNSR	GENCGYRRCR	2700
ASGVLTTSCG	NTLTCYIKAR	AACRAAGLQD	CTMLVCGDDL	VVICESAGVQ	2750
EDAASLRAFT	EAMTRYSAPP	GDPPQPEYDL	ELITSCSSNV	SVAHDGAGKR	2800
VYYLTRDPTT	PLARAAWETA	RHTPVNSWLG	NIIMFAPTLW	ARMILMTHFF	2850
SVLIARDQLE	QALNCEIYGA	CYSIEPLDLP	PIIQRLHGLS	AFSLHSYSPG	2900
EINRVAACLR	KLGVPPLRAW	RHRARSVRAR	LLSRGGRAAI	CGKYLFNWAV	2950
RTKLKLTPIA	AAGRLDLSGW	FTAGYSGGDI	YHSVSHARPR	WFWFCLLLLA	3000
AGVGIYLLPN	R				3011

FIG. 6H

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATCAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCGAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GCCGCCCACA	400
GGACGTCAAG	TTCCCGGGCG	GTGGTCAGAT	CGTTGGTGGA	GTTTACCTGT	450
TGCCGCGCAG	GGGCCCCAGG	TTGGGTGTGC	GCGCGACTAG	GAAGGCTTCC	500
GAGCGGTCGC	AACCTCGTGG	AAGGCGACAA	CCTATCCCAA	AGGCTCGCCG	550
ACCCGAGGGC	AGGGCCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	CCTGGGGTGG	GCAGGATGGC	TCCTGTCACC	CCGCGGCTCC	650
CGGCCTAGTT	GGGGCCCCAC	GGACCCCCGG	CGTAGGTCGC	GTAACTTGGG	700
TAAGGTCATC	GATACCCTTA	CATGCGGCTT	CGCCGATCTC	ATGGGGTACA	750
TTCCGCTCGT	CGGCGCCCCC	CTAGGGGGCG	CTGCCAGGGC	CTTGGCACAC	800
GGTGTCCGGG	TTCTGGAGGA	CGGCGTGAAC	TATGCAACAG	GGAACTTGCC	850
CGGTTGCTCT	TTCTCTATCT	TCCTCTTGGC	TCTGCTGTCC	TGTTTGACCA	900
TCCCAGCTTC	CGCTTATGAA	GTGCGCAACG	TGTCCGGGAT	ATACCATGTC	950
ACGAACGACT	GCTCCAACTC	AAGCATTGTG	TATGAGGCAG	CGGACGTGAT	1000
CATGCATACT	CCCGGGTGCG	TGCCCTGTGT	TCAGGAGGGT	AACAGCTCCC	1050
GTTGCTGGGT	AGCGCTCACT	CCCACGCTCG	CGGCCAGGAA	TGCCAGCGTC	1100
CCCACTACGA	CAATACGACG	CCACGTCGAC	TTGCTCGTTG	GGACGGCTGC	1150
TTTCTGCTCC	GCTATGTACG	TGGGGGATCT	CTGCGGATCT	ATTTTCCTCG	1200
TCTCCCAGCT	GTTCACCTTC	TCGCCTCGCC	GGCATGAGAC	AGTGCAGGAC	1250
TGCAACTGCT	CAATCTATCC	CGGCCATGTA	TCAGGTCACC	GCATGGCTTG	1300
GGATATGATG	ATGAACTGGT	CACCTACAAC	AGCCCTAGTG	GTGTCGCAGT	1350
TGCTCCGGAT	CCCACAAGCT	GTCGTGGACA	TGGTGGCGGG	GGCCCACTGG	1400
GGAGTCCTGG	CGGGCCTTGC	CTACTATTCC	ATGGTAGGGA	ACTGGGCTAA	1450
GGTTCTGATT	GTGGCGCTAC	TCTTTGCCGG	CGTTGACGGG	GAGACCCACA	1500
CGACGGGGAG	GGTGGCCGGC	CACACCACCT	CCGGGTTCAC	GTCCCTTTTC	1550
TCATCTGGGG	CGTCTCAGAA	AATCCAGCTT	GTGAATACCA	ACGGCAGCTG	1600
GCACATCAAC	AGGACTGCCC	TAAATTGCAA	TGACTCCCTC	CAAACTGGGT	1650
TCTTTGCCGC	GCTGTTTTAC	GCACACAAGT	TCAACTCGTC	CGGGTGCCCG	1700
GAGCGCATGG	CCAGCTGCCG	CCCCATTGAC	TGGTTCGCCC	AGGGGTGGGG	1750
CCCCATCACC	TATACTAAGC	CTAACAGCTC	GGATCAGAGG	CCTTATTGCT	1800
GGCATTACGC	GCCTCGACCG	TGTGGTGTCG	TACCCGCGTC	GCAGGTGTGT	1850
GGTCCAGTGT	ATTGTTTCAC	CCCAAGCCCT	GTTGTGGTGG	GGACCACCGA	1900

FIG. 7A

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGTTCCGGT	GTCCCTACGT	ATAGCTGGGG	GGAGAATGAG	ACAGACGTGA	1950
TGCTCCTCAA	CAACACGCGT	CCGCCACAAG	GCAACTGGTT	CGGCTGTACA	2000
TGGATGAATA	GTACTGGGTT	CACTAAGACG	TGCGGAGGTC	CCCCGTGTAA	2050
CATCGGGGGG	GTCGGTAACC	GCACCTTGAT	CTGCCCCACG	GACTGCTTCC	2100
GGAAGCACCC	CGAGGCTACT	TACACAAAAT	GTGGCTCGGG	GCCCTGGTTG	2150
ACACCTAGGT	GCCTAGTAGA	CTACCCATAC	AGGCTTTGGC	ACTACCCCTG	2200
CACTCTCAAT	TTTTCCATCT	TTAAGGTTAG	GATGTATGTG	GGGGGCGTGG	2250
AGCACAGGCT	CAATGCCGCA	TGCAATTGGA	CTCGAGGAGA	GCGCTGTAAC	2300
TTGGAGGACA	GGGATAGGTC	AGAACTCAGC	CCGCTGCTGC	TGTCTACAAC	2350
AGAGTGGCAG	ATACTGCCCT	GTGCTTTCAC	CACCCTACCG	GCTTTATCCA	2400
CTGGTTTGAT	CCATCTCCAT	CAGAACATCG	TGGACGTGCA	ATACCTGTAC	2450
GGTGTAGGGT	CAGCGTTTGT	CTCCTTTGCA	ATCAAATGGG	AGTACATCCT	2500
GTTGCTTTTC	CTTCTCCTGG	CAGACGCGCG	CGTGTGTGCC	TGCTTGTGGA	2550
TGATGCTGCT	GATAGCCCAG	GCTGAGGCCG	CCTTAGAGAA	CTTGGTGGTC	2600
CTCAATGCGG	CGTCCGTGGC	CGGAGCGCAT	GGTATTCTCT	CCTTTCTTGT	2650
GTTCTTCTGC	GCCGCCTGGT	ACATTAAGGG	CAGGCTGGCT	CCTGGGGCGG	2700
CGTATGCTTT	TTATGGCGTA	TGGCCGCTGC	TCCTGCTCCT	ACTGGCGTTA	2750
CCACCACGAG	CTTACGCCTT	GGACCGGGAG	ATGGCTGCAT	CGTGCGGGGG	2800
TGCGGTTCTT	GTAGGTCTGG	TATTCTTGAC	CTTGTCACCA	TACTACAAAG	2850
TGTTTCTCAC	TAGGCTCATA	TGGTGGTTAC	AATACTTTAT	CACCAGAGCC	2900
GAGGCGCACA	TGCAAGTGTG	GGTCCCCCCC	CTCAACGTTC	GGGGAGGCCG	2950
CGATGCCATC	ATCCTCCTCA	CGTGTGCGGT	TCATCCAGAG	TTAATTTTTG	3000
ACATCACCAA	ACTCCTGCTC	GCCATACTCG	GCCCGCTCAT	GGTGCTCCAG	3050
GCTGGCATAA	CGAGAGTGCC	GTACTTCGTG	CGCGCTCAAG	GGCTCATTCG	3100
TGCATGCATG	TTAGTGCGAA	AAGTCGCCGG	GGGTCATTAT	GTCCAAATGG	3150
TCTTCATGAA	GCTGGCCGCG	CTGACAGGTA	CGTACGTTTA	TAACCATCTT	3200
ACCCCACTGC	GGGACTGGGC	CCACGCGGGC	CTACGAGACC	TTGCGGTGGC	3250
GGTAGAGCCC	GTCGTCTTCT	CCGCCATGGA	GACCAAGGTC	ATCACCTGGG	3300
GAGCAGACAC	CGCTGCGTGT	GGGGACATCA	TCTTGGGTCT	ACCCGTCTCC	3350
GCCCGAAGGG	GGAAGGAGAT	ATTTTTGGGA	CCGGCTGATA	GTCTCGAAGG	3400
GCAAGGGTGG	CGACTCCTTG	CGCCCATCAC	GGCCTACTCC	CAACAAACGC	3450
GGGGCGTACT	TGGTTGCATC	ATCACTAGCC	TCACAGGCCG	GGACAAGAAC	3500
CAGGTCGAAG	GGGAGGTTCA	AGTGGTTTCT	ACCGCAACAC	AATCTTTCCT	3550
GGCGACCTGC	ATCAACGGCG	TGTGCTGGAC	TGTCTACCAT	GGCGCTGGCT	3600
CGAAGACCCT	AGCCGGTCCA	AAAGGTCCAA	TCACCCAAAT	GTACACCAAT	3650
GTAGACCTGG	ACCTCGTCGG	CTGGCAGGCG	CCCCCCGGGG	CGCGCTCCAT	3700
GACACCATGC	AGCTGTGGCA	GCTCGGACCT	TTACTTGGTC	ACGAGACATG	3750
CTGATGTCAT	TCCGGTGCGC	CGGCGAGGCG	ACAGCAGGGG	AAGTCTACTC	3800

FIG. 7B

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCCCCCAGGC	CCGTCTCCTA	CCTGAAAGGC	TCCTCGGGTG	GTCCATTGCT	3850
TTGCCCTTCG	GGGCACGTCG	TGGGCGTCTT	CCGGGCTGCT	GTGTGCACCC	3900
GGGGGGTCGC	GAAGGCGGTG	GACTTCATAC	CCGTTGAGTC	TATGGAAACT	3950
ACCATGCGGT	CTCCGGTCTT	CACAGACAAC	TCAACCCCCC	CGGCTGTACC	4000
GCAGACATTC	CAAGTGGCAC	ATCTGCACGC	TCCTACTGGC	AGCGGCAAGA	4050
GCACCAAAGT	GCCGGCTGCG	TATGCAGCCC	AAGGGTACAA	GGTGCTCGTC	4100
CTGAACCCGT	CCGTTGCCGC	CACCTTAGGG	TTTGGGGCGT	ATATGTCCAA	4150
GGCACACGGT	ATCGACCCTA	ACATCAGAAC	TGGGGTAAGG	ACCATTACCA	4200
CGGGCGGCTC	CATTACGTAC	TCCACCTATG	GCAAGTTCCT	TGCCGACGGT	4250
GGCTGTTCTG	GGGGCGCCTA	TGACATCATA	ATATGTGATG	AGTGCCACTC	4300
AACTGACTCG	ACTACCATCT	TGGGCATCGG	CACAGTCCTG	GACCAAGCGG	4350
AGACGGCTGG	AGCGCGGCTC	GTCGTGCTCG	CCACCGCTAC	ACCTCCGGGA	4400
TCGGTTACCG	TGCCACACCC	CAATATCGAG	GAAATAGGCC	TGTCCAACAA	4450
TGGAGAGATC	CCCTTCTATG	GCAAAGCCAT	CCCCATTGAG	GCCATCAAGG	4500
GGGGGAGGCA	TCTCATTTTC	TGCCATTCCA	AGAAGAAATG	TGACGAGCTC	4550
GCCGCAAAGC	TGACAGGCCT	CGGACTGAAC	GCTGTAGCAT	ATTACCGGGG	4600
CCTTGATGTG	TCCGTCATAC	CGCCTATCGG	AGACGTCGTT	GTCGTGGCAA	4650
CAGACGCTCT	AATGACGGGT	TTCACCGGCG	ATTTTGACTC	AGTGATCGAC	4700
TGCAATACAT	GTGTCACCCA	GACAGTCGAC	TTCAGCTTGG	ATCCCACCTT	4750
CACCATTGAG	ACGACGACCG	TGCCCCAAGA	CGCGGTGTCG	CGCTCGCAAC	4800
GGCGAGGTAG	AACTGGCAGG	GGTAGGAGTG	GCATCTACAG	GTTTGTGACT	4850
CCAGGAGAAC	GGCCCTCGGG	CATGTTCGAT	TCTTCGGTCC	TGTGTGAGTG	4900
CTATGACGCG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCT	GAGACCTCGG	4950
TTAGGTTGCG	GGCTTACCTA	AATACACCAG	GGTTGCCCGT	CTGCCAGGAC	5000
CATCTGGAGT	TCTGGGAGAG	CGTCTTCACA	GGCCTCACCC	ACATAGATGC	5050
CCACTTCCTG	TCCCAGACTA	AACAGGCAGG	AGACAACTTT	CCTTACCTGG	5100
TGGCATATCA	AGCTACAGTG	TGCGCCAGGG	CTCAAGCTCC	ACCTCCATCG	5150
TGGGACCAAA	TGTGGAAGTG	TCTCATACGG	CTGAAACCTA	CACTGCACGG	5200
GCCAACACCC	CTGCTGTATA	GGCTAGGAGC	CGTCCAAAAT	GAGGTCATCC	5250
TCACACACCC	CATAACTAAA	TACATCATGG	CATGCATGTC	GGCTGACCTG	5300
GAGGTCGTCA	CTAGCACCTG	GGTGCTGGTA	GGCGGAGTCC	TTGCAGCTTT	5350
GGCCGCATAC	TGCCTGACGA	CAGGCAGTGT	GGTCATTGTG	GGCAGGATCA	5400
TCTTGTCCGG	GAAGCCAGCT	GTCGTTCCCG	ACAGGGAAGT	CCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGTGCCTCA	CAACTTCCTT	ACATCGAGCA	5500
GGGAATGCAG	CTCGCCGAGC	AATTCAAGCA	AAAGGCGCTC	GGGTTGTTGC	5550
AAACGGCCAC	CAAGCAAGCG	GAGGCTGCTG	CTCCCGTGGT	GGAGTCCAAG	5600
TGGCGAGCCC	TTGAGACCTT	CTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
CGGAATACAG	TACCTAGCAG	GCTTATCCAC	TCTGCCTGGA	AACCCCGCGA	5700

FIG. 7C

HC-J4

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
TAGCATCATT	GATGGCATTT	ACAGCTTCTA	TCACTAGCCC	GCTCACCACC	5750
CAAAACACCC	TCCTGTTTAA	CATCTTGGGG	GGATGGGTGG	CTGCCCAACT	5800
CGCTCCTCCC	AGCGCTGCGT	CAGCTTTCGT	GGGCGCCGGC	ATCGCCGGAG	5850
CGGCTGTTGG	CAGCATAGGC	CTTGGGAAGG	TGCTCGTGGA	CATCTTGGCG	5900
GGCTATGGGG	CAGGGGTAGC	CGGCGCACTC	GTGGCCTTTA	AGGTCATGAG	5950
CGGCGAGGTG	CCCTCCACCG	AGGACCTGGT	CAACTTACTC	CCTGCCATCC	6000
TCTCTCCTGG	TGCCCTGGTC	GTCGGGGTCG	TGTGCGCAGC	AATACTGCGT	6050
CGGCACGTGG	GCCCGGGAGA	GGGGGCTGTG	CAGTGGATGA	ACCGGCTGAT	6100
AGCGTTCGCT	TCGCGGGGTA	ACCACGTCTC	CCCTACGCAC	TATGTGCCTG	6150
AGAGCGACGC	TGCAGCACGT	GTCACTCAGA	TCCTCTCTAG	CCTTACCATC	6200
ACTCAACTGC	TGAAGCGGCT	CCACCAGTGG	ATTAATGAGG	ACTGCTCTAC	6250
GCCATGCTCC	GGCTCGTGGC	TAAGGGATGT	TTGGGATTGG	ATATGCACGG	6300
TGTTGACTGA	CTTCAAGACC	TGGCTCCAGT	CCAAACTCCT	GCCGCGGTTA	6350
CCGGGAGTCC	CTTTCCTGTC	ATGCCAACGC	GGGTACAAGG	GAGTCTGGCG	6400
GGGGGACGGC	ATCATGCAAA	CCACCTGCCC	ATGCGGAGCA	CAGATCGCCG	6450
GACATGTCAA	AAACGGTTCC	ATGAGGATCG	TAGGGCCTAG	AACCTGCAGC	6500
AACACGTGGC	ACGGAACGTT	CCCCATCAAC	GCATACACCA	CGGGACCTTG	6550
CACACCCTCC	CCGGCGCCCA	ACTATTCCAG	GGCGCTATGG	CGGGTGGCTG	6600
CTGAGGAGTA	CGTGGAGGTT	ACGCGTGTGG	GGGATTTCCA	CTACGTGACG	6650
GGCATGACCA	CTGACAACGT	AAAGTGCCCA	TGCCAGGTTC	CGGCCCCCGA	6700
ATTCTTCACG	GAGGTGGATG	GAGTGCGGTT	GCACAGGTAC	GCTCCGGCGT	6750
GCAAACCTCT	TCTACGGGAG	GACGTCACGT	TCCAGGTCGG	GCTCAACCAA	6800
TACTTGGTCG	GGTCGCAGCT	CCCATGCGAG	CCCGAACCGG	ACGTAACAGT	6850
GCTTACTTCC	ATGCTCACCG	ATCCCTCCCA	CATTACAGCA	GAGACGGCTA	6900
AGCGTAGGCT	GGCTAGAGGG	TCTCCCCCCT	CTTTAGCCAG	CTCATCAGCT	6950
AGCCAGTTGT	CTGCGCCTTC	TTTGAAGGCG	ACATGCACTA	CCCACCATGA	7000
CTCCCCGGAC	GCTGACCTCA	TCGAGGCCAA	CCTCTTGTGG	CGGCAGGAGA	7050
TGGCGGGAAA	CATCACTCGC	GTGGAGTCAG	AGAATAAGGT	AGTAATTCTG	7100
GACTCTTTCG	AACCGCTTCA	CGCGGAGGGG	GATGAGAGGG	AGATATCCGT	7150
CGCGGCGGAG	ATCCTGCGAA	AATCCAGGAA	GTTCCCCTCA	GCGTTGCCCA	7200
TATGGGCACG	CCCGGACTAC	AATCCTCCAC	TGCTAGAGTC	CTGGAAGGAC	7250
CCGGACTACG	TCCCTCCGGT	GGTACACGGA	TGCCCATTGC	CACCTACCAA	7300
GGCTCCTCCA	ATACCACCTC	CACGGAGAAA	GAGGACGGTT	GTCCTGACAG	7350
AATCCAATGT	GTCTTCTGCC	TTGGCGGAGC	TCGCCACTAA	GACCTTCGGT	7400
AGCTCCGGAT	CGTCGGCCGT	TGATAGCGGC	ACGGCGACCG	CCCTTCCTGA	7450
CCTGGCCTCC	GACGACGGTG	ACAAAGGATC	CGACGTTGAG	TCGTACTCCT	7500
CCATGCCCCC	CCTTGAAGGG	GAGCCGGGGG	ACCCCGATCT	CAGCGACGGG	7550
TCTTGGTCTA	CCGTGAGTGA	GGAGGCTAGT	GAGGATGTCG	TCTGCTGCTC	7600

FIG. 7D

HC-J4

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
AATGTCCTAT	ACGTGGACAG	GCGCCCTGAT	CACGCCATGC	GCTGCGGAGG	7650
AAAGTAAGCT	GCCCATCAAC	CCGTTGAGCA	ACTCTTTGCT	GCGTCACCAC	7700
AACATGGTCT	ACGCCACAAC	ATCCCGCAGC	GCAAGCCTCC	GGCAGAAGAA	7750
GGTCACCTTT	GACAGATTGC	AAGTCCTGGA	TGATCATTAC	CGGGACGTAC	7800
TCAAGGAGAT	GAAGGCGAAG	GCGTCCACAG	TTAAGGCTAA	GCTTCTATCT	7850
ATAGAGGAGG	CCTGCAAGCT	GACGCCCCCA	CATTCGGCCA	AATCCAAATT	7900
TGGCTATGGG	GCAAAGGACG	TCCGGAACCT	ATCCAGCAGG	GCCGTTAACC	7950
ACATCCGCTC	CGTGTGGGAG	GACTTGCTGG	AAGACACTGA	AACACCAATT	8000
GACACCACCA	TCATGGCAAA	AAGTGAGGTT	TTCTGCGTCC	AACCAGAGAA	8050
GGGAGGCCGC	AAGCCAGCTC	GCCTTATCGT	ATTCCCAGAC	CTGGGAGTTC	8100
GTGTATGCGA	GAAGATGGCC	CTTTACGACG	TGGTCTCCAC	CCTTCCTCAG	8150
GCCGTGATGG	GCTCCTCATA	CGGATTTCAA	TACTCCCCCA	AGCAGCGGGT	8200
CGAGTTCCTG	GTGAATACCT	GGAAATCAAA	GAAATGCCCT	ATGGGCTTCT	8250
CATATGACAC	CCGCTGTTTT	GACTCAACGG	TCACTGAGAG	TGACATTCGT	8300
GTTGAGGAGT	CAATTTACCA	ATGTTGTGAC	TTGGCCCCCG	AGGCCAGACA	8350
GGCCATAAGG	TCGCTCACAG	AGCGGCTTTA	CATCGGGGGT	CCCCTGACTA	8400
ACTCAAAAGG	GCAGAACTGC	GGTTATCGCC	GGTGCCGCGC	AAGTGGCGTG	8450
CTGACGACTA	GCTGCGGTAA	TACCCTCACA	TGTTACTTGA	AGGCCACTGC	8500
AGCCTGTCGA	GCTGCAAAGC	TCCAGGACTG	CACGATGCTC	GTGAACGGAG	8550
ACGACCTTGT	CGTTATCTGT	GAAAGCGCGG	GAACCCAGGA	GGATGCGGCG	8600
GCCCTACGAG	CCTTCACGGA	GGCTATGACT	AGGTATTCCG	CCCCCCCCGG	8650
GGATCCGCCC	CAACCAGAAT	ACGACCTGGA	GCTGATAACA	TCATGTTCCT	8700
CCAATGTGTC	AGTCGCGCAC	GATGCATCTG	GCAAAAGGGT	ATACTACCTC	8750
ACCCGTGACC	CCACCACCCC	CCTTGCACGG	GCTGCGTGGG	AGACAGCTAG	8800
ACACACTCCA	ATCAACTCTT	GGCTAGGCAA	TATCATCATG	TATGCGCCCA	8850
CCCTATGGGC	AAGGATGATT	CTGATGACTC	ACTTTTTCTC	CATCCTTCTA	8900
GCTCAAGAGC	AACTTGAAAA	AGCCCTGGAT	TGTCAGATCT	ACGGGGCTTG	8950
CTACTCCATT	GAGCCACTTG	ACCTACCTCA	GATCATTGAA	CGACTCCATG	9000
GTCTTAGCGC	ATTTACACTC	CACAGTTACT	CTCCAGGTGA	GATCAATAGG	9050
GTGGCTTCAT	GCCTCAGGAA	ACTTGGGGTA	CCACCCTTGC	GAACCTGGAG	9100
ACATCGGGCC	AGAAGTGTCC	GCGCTAAGCT	ACTGTCCCAG	GGGGGGAGGG	9150
CCGCCACTTG	TGGCAGATAC	CTCTTTAACT	GGGCAGTAAG	GACCAAGCTT	9200
AAACTCACTC	CAATCCCGGC	CGCGTCCCAG	CTGGACTTGT	CTGGCTGGTT	9250
CGTCGCTGGT	TACAGCGGGG	GAGACATATA	TCACAGCCTG	TCTCGTGCCC	9300
GACCCCGCTG	GTTTCCGTTG	TGCCTACTCC	TACTTTCTGT	AGGGGTAGGC	9350
ATTTACCTGC	TCCCCAACCG	ATGAACGGGG	AGCTAACCAC	TCCAGGCCTT	9400
AAGCCATTTC	CTGTTTTTTT	TTTTTTTTTT	TTTTTTTTTT	TCTTTTTTTT	9450
TTTCTTTCCT	TTCCTTCTTT	TTTTCCTTTC	TTTTTCCCTT	CTTTAATGGT	9500

FIG. 7E

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGCTCCATCT	TAGCCCTAGT	CACGGCTAGC	TGTGAAAGGT	CCGTGAGCCG	9550
CATGACTGCA	GAGAGTGCTG	ATACTGGCCT	CTCTGCAGAT	CATGT	9595

FIG. 7F

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
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KASERSQPRG	RRQPIPKARR	PEGRAWAQPG	YPWPLYGNEG	LGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTIPAS	AYEVRNVSGI	200
YHVTNDCSNS	SIVYEAADVI	MHTPGCVPCV	QEGNSSRCWV	ALTPTLAARN	250
ASVPTTTIRR	HVDLLVGTAA	FCSAMYVGDL	CGSIFLVSQL	FTFSPRRHET	300
VQDCNCSIYP	GHVSGHRMAW	DMMMNWSPTT	ALVVSQLLRI	PQAVVDMVAG	350
AHWGVLAGLA	YYSMVGNWAK	VLIVALLFAG	VDGETHTTGR	VAGHTTSGFT	400
SLFSSGASQK	IQLVNTNGSW	HINRTALNCN	DSLQTGFFAA	LFYAHKFNSS	450
GCPERMASCR	PIDWFAQGWG	PITYTKPNSS	DQRPYCWHYA	PRPCGVVPAS	500
QVCGPVYCFT	PSPVVVGTTD	RSGVPTYSWG	ENETDVMLLN	NTRPPQGNWF	550
GCTWMNSTGF	TKTCGGPPCN	IGGVGNRTLI	CPTDCFRKHP	EATYTKCGSG	600
PWLTPRCLVD	YPYRLWHYPC	TLNFSIFKVR	MYVGGVEHRL	NAACNWTRGE	650
RCNLEDRDRS	ELSPLLLSTT	EWQILPCAFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSAFV	SFAIKWEYIL	LLFLLLADAR	VCACLWMMLL	IAQAEAALEN	750
LVVLNAASVA	GAHGILSFLV	FFCAAWYIKG	RLAPGAAYAF	YGVWPLLLLL	800
LALPPRAYAL	DREMAASCGG	AVLVGLVFLT	LSPYYKVFLT	RLIWWLQYFI	850
TRAEAHMQVW	VPPLNVRGGR	DAIILLTCAV	HPELIFDITK	LLLAILGPLM	900
VLQAGITRVP	YFVRAQGLIR	ACMLVRKVAG	GHYVQMVFMK	LGALTGTYVY	950
NHLTPLRDWA	HAGLRDLAVA	VEPVVFSAME	TKVITWGADT	AACGDIILGL	1000
PVSARRGKEI	FLGPADSLEG	QGWRLLAPIT	AYSQQTRGVL	GCIITSLTGR	1050
DKNQVEGEVQ	VVSTATQSFL	ATCINGVCWT	VYHGAGSKTL	AGPKGPITQM	1100
YTNVDLDLVG	WQAPPGARSM	TPCSCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPVSY	LKGSSGGPLL	CPSGHVVGVF	RAAVCTRGVA	KAVDFIPVES	1200
METTMRSPVF	TDNSTPPAVP	QTFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGIDPNIRT	GVRTITTGGS	ITYSTYGKFL	1300
ADGGCSGGAY	DIIICDECHS	TDSTTILGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVPHP	NIEEIGLSNN	GEIPFYGKAI	PIEAIKGGRH	LIFCHSKKKC	1400
DELAAKLTGL	GLNAVAYYRG	LDVSVIPPIG	DVVVVATDAL	MTGFTGDFDS	1450
VIDCNTCVTQ	TVDFSLDPTF	TIETTTVPQD	AVSRSQRRGR	TGRGRSGIYR	1500
FVTPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETSVRLR	AYLNTPGLPV	1550
CQDHLEFWES	VFTGLTHIDA	HFLSQTKQAG	DNFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVILTHP	ITKYIMACMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLTTGSV	VIVGRIILSG	KPAVVPDREV	1700
LYQEFDEMEE	CASQLPYIEQ	GMQLAEQFKQ	KALGLLQTAT	KQAEAAAPVV	1750
ESKWRALETF	WAKHMWNFIS	GIQYLAGLST	LPGNPAIASL	MAFTASITSP	1800
LTTQNTLLFN	ILGGWVAAQL	APPSAASAFV	GAGIAGAAVG	SIGLGKVLVD	1850
ILAGYGAGVA	GALVAFKVMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVVCAA	1900

FIG. 7G

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPGE	GAVQWMNRLI	AFASRGNHVS	PTHYVPESDA	AARVTQILSS	1950
LTITQLLKRL	HQWINEDCST	PCSGSWLRDV	WDWICTVLTD	FKTWLQSKLL	2000
PRLPGVPFLS	CQRGYKGVWR	GDGIMQTTCP	CGAQIAGHVK	NGSMRIVGPR	2050
TCSNTWHGTF	PINAYTTGPC	TPSPAPNYSR	ALWRVAAEEY	VEVTRVGDFH	2100
YVTGMTTDNV	KCPCQVPAPE	FFTEVDGVRL	HRYAPACKPL	LREDVTFQVG	2150
LNQYLVGSQL	PCEPEPDVTV	LTSMLTDPSH	ITAETAKRRL	ARGSPPSLAS	2200
SSASQLSAPS	LKATCTTHHD	SPDADLIEAN	LLWRQEMGGN	ITRVESENKV	2250
VILDSFEPLH	AEGDEREISV	AAEILRKSRK	FPSALPIWAR	PDYNPPLLES	2300
WKDPDYVPPV	VHGCPLPPIK	APPIPPPRRK	RTVVLTESNV	SSALAELATK	2350
TFGSSGSSAV	DSGTATALPD	LASDDGDKGS	DVESYSSMPP	LEGEPGDPDL	2400
SDGSWSTVSE	EASEDVVCCS	MSYTWTGALI	TPCAAEESKL	PINPLSNSLL	2450
RHHNMVYATT	SRSASLRQKK	VTFDRLQVLD	DHYRDVLKEM	KAKASTVKAK	2500
LLSIEEACKL	TPPHSAKSKF	GYGAKDVRNL	SSRAVNHIRS	VWEDLLEDTE	2550
TPIDTTIMAK	SEVFCVQPEK	GGRKPARLIV	FPDLGVRVCE	KMALYDVVST	2600
LPQAVMGSSY	GFQYSPKQRV	EFLVNTWKSK	KCPMGFSYDT	RCFDSTVTES	2650
DIRVEESIYQ	CCDLAPEARQ	AIRSLTERLY	IGGPLTNSKG	QNCGYRRCRA	2700
SGVLTTSCGN	TLTCYLKATA	ACRAAKLQDC	TMLVNGDDLV	VICESAGTQE	2750
DAAALRAFTE	AMTRYSAPPG	DPPQPEYDLE	LITSCSSNVS	VAHDASGKRV	2800
YYLTRDPTTP	LARAAWETAR	HTPINSWLGN	IIMYAPTLWA	RMILMTHFFS	2850
ILLAQEQLEK	ALDCQIYGAC	YSIEPLDLPQ	IIERLHGLSA	FTLHSYSPGE	2900
INRVASCLRK	LGVPPLRTWR	HRARSVRAKL	LSQGGRAATC	GRYLFNWAVR	2950
TKLKLTPIPA	ASQLDLSGWF	VAGYSGGDIY	HSLSRARPRW	FPLCLLLLSV	3000
GVGIYLLPNR					3010

FIG. 7H

SEQUENCE LISTING

<110> Yanagi, Masayuki
Emerson, Suzanne
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Purcell, Robert

<120> Cloned Genome of Infectious Hepatitis C Viruses of
Genotype 2a and Uses Thereof

<130> 20264302PC

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<141> 2000-06-02

<150> 60/137,693
<151> 1999-06-04

<160> 39

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Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
        35   40   45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
    50   55   60

Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
65   70   75   80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
                85   90   95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
            100   105   110

Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
        115   120   125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
    130   135   140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145   150   155   160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
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Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
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Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
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Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
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Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
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Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
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755 760 765

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850 855 860

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1845 1850 1855

Ala Gly Tyr Gly Ala Gly Ile Ser Gly Ala Leu Val Ala Phe Lys Ile
1860 1865 1870

Met Ser Gly Glu Lys Pro Ser Met Glu Asp Val Val Asn Leu Leu Pro
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Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met
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Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
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Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
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Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
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Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
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His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr

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755 760 765

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Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu
915 920 925

Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala Ile Ile Lys
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Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
        35   40   45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
    50   55   60

Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
65   70   75   80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
                85   90   95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
            100   105   110

Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
        115   120   125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
    130   135   140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145   150   155   160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
                165   170   175

Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
            180   185   190

Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
        195   200   205

Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
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Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile
225 230 235 240

Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln
245 250 255

Gly Leu Arg Thr His Ile Asp Met Val Val Met Ser Ala Thr Leu Cys
260 265 270

Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala
275 280 285

Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys
290 295 300

Asn Cys Ser Ile Tyr Pro Gly Thr Ile Thr Gly His Arg Met Ala Trp
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Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr
325 330 335

Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His
340 345 350

Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp
355 360 365

Ala Lys Val Val Val Ile Leu Leu Leu Ala Ala Gly Val Asp Ala Arg
370 375 380

Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr
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Ser Leu Phe Asp Met Gly Pro Arg Gln Lys Ile Gln Leu Val Asn Thr
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Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu Asn Cys Asn Asp Ser
420 425 430

Leu His Thr Gly Phe Ile Ala Ser Leu Phe Tyr Thr His Ser Phe Asn
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Ser Ser Gly Cys Pro Glu Arg Met Ser Ala Cys Arg Ser Ile Glu Ala
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Phe Arg Val Gly Trp Gly Ala Leu Gln Tyr Glu Asp Asn Val Thr Asn
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Pro Glu Asp Met Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Gln Cys
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Gly Val Val Ser Ala Lys Thr Val Cys Gly Pro Val Tyr Cys Phe Thr
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Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr
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Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr
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Arg Pro Pro Leu Gly Ser Trp Phe Gly Cys Thr Trp Met Asn Ser Ser
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Gly Tyr Thr Lys Thr Cys Gly Ala Pro Pro Cys Arg Thr Arg Ala Asp
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Phe Asn Ala Ser Thr Asp Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys
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His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr
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Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
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Thr Val Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val
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Glu His Arg Leu Thr Ala Ala Cys Asn Phe Thr Arg Gly Asp Arg Cys
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Asn Leu Glu Asp Arg Asp Arg Ser Gln Leu Ser Pro Leu Leu His Ser
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Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
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Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
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Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
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Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
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Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu
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Glu Asn Leu Val Ile Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly
755 760 765

Leu Val Ser Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly
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Arg Trp Val Pro Gly Ala Val Tyr Ala Leu Tyr Gly Met Trp Pro Leu
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Leu Leu Leu Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr
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Glu Val Ala Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala
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Leu Thr Leu Ser Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp Cys Met Trp
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Trp Leu Gln Tyr Phe Leu Thr Arg Val Glu Ala Gln Leu His Val Trp
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Val Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val Ile Leu Leu
865 870 875 880

Met Cys Val Val His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu
885 890 895

Leu Ala Ile Phe Gly Pro Leu Trp Ile Leu Gln Ala Ser Leu Leu Lys
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Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu
915 920 925

Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala Ile Ile Lys
930 935 940

Leu Gly Ala Leu Thr Gly Thr Tyr Val Tyr Asn His Leu Thr Pro Leu
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Arg Asp Trp Ala His Asn Gly Leu Arg Asp Leu Ala Val Ala Val Glu
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Pro Val Val Phe Ser Arg Met Glu Thr Lys Leu Ile Thr Trp Gly Ala
980 985 990

Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala
995 1000 1005

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Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr
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Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser
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Arg Gly Ser Leu Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser
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Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Ile
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Pro Val Glu Asn Leu Gly Thr Thr Met Arg Ser Pro Val Phe Thr Asp
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His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr
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Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr
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Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly
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Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr
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Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly
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Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr
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Val Ser His Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu
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Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly
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Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala
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Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly
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Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Val Val Val Ser
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Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp Ser Val Ile
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Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro
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Thr Phe Thr Ile Glu Thr Thr Thr Leu Pro Gln Asp Ala Val Ser Arg
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Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg
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Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly
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Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly
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Glu Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg
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Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile
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Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu
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Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr
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Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp
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Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser
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Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro
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Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln Glu Phe Asp Glu Met
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Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu
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Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser
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Arg His Ala Glu Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys
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Leu Glu Val Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile
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Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala
1780 1785 1790

Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly
1795 1800 1805

Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu
1810 1815 1820

Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly
1825 1830 1835 1840

Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu
1845 1850 1855

Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile
1860 1865 1870

Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro
1875 1880 1885

Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala
1890 1895 1900

Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met
1905 1910 1915 1920

Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr
1925 1930 1935

His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu
1940 1945 1950

Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile
1955 1960 1965

Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile
1970 1975 1980

Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys
1985 1990 1995 2000

Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln
2005 2010 2015

Arg Gly Tyr Arg Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg
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Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys Asn Gly Thr Met
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Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe
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Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro
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Asn Tyr Lys Phe Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu
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Ile Arg Arg Val Gly Asp Phe His Tyr Val Ser Gly Met Thr Thr Asp
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Asn Leu Lys Cys Pro Cys Gln Ile Pro Ser Pro Glu Phe Phe Thr Glu
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Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg
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Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Ala Asn His Asp
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Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu
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Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile
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Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg Phe Ala Arg Ala
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Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu
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Pro Pro Pro Arg Ser Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr
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Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala
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Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg
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Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly
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Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr
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Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu
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Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly
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Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu
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Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys
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Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala
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Arg Ser Val Arg Ala Arg Leu Leu Ser Arg Gly Gly Arg Ala Ala Ile
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Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu
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Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val Ser His Ala Arg
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Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
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Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
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Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
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Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145 150 155 160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
180 185 190

Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
195 200 205

Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
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Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile

225 230 235 240

Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln
245 250 255

Gly Leu Arg Thr His Ile Asp Met Val Val Met Ser Ala Thr Leu Cys
260 265 270

Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala
275 280 285

Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys
290 295 300

Asn Cys Ser Ile Tyr Pro Gly Thr Ile Thr Gly His Arg Met Ala Trp
305 310 315 320

Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr
325 330 335

Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His
340 345 350

Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp
355 360 365

Ala Lys Val Val Val Ile Leu Leu Leu Ala Ala Gly Val Asp Ala Arg
370 375 380

Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr
385 390 395 400

Ser Leu Phe Asp Met Gly Pro Arg Gln Lys Ile Gln Leu Val Asn Thr
405 410 415

Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu Asn Cys Asn Asp Ser
420 425 430

Leu His Thr Gly Phe Ile Ala Ser Leu Phe Tyr Thr His Ser Phe Asn
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Ser Ser Gly Cys Pro Glu Arg Met Ser Ala Cys Arg Ser Ile Glu Ala
450 455 460

Phe Arg Val Gly Trp Gly Ala Leu Gln Tyr Glu Asp Asn Val Thr Asn
465 470 475 480

Pro Glu Asp Met Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Gln Cys

485 490 495

Gly Val Val Ser Ala Lys Thr Val Cys Gly Pro Val Tyr Cys Phe Thr
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Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr
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Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr
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Arg Pro Pro Leu Gly Ser Trp Phe Gly Cys Thr Trp Met Asn Ser Ser
545 550 555 560

Gly Tyr Thr Lys Thr Cys Gly Ala Pro Pro Cys Arg Thr Arg Ala Asp
565 570 575

Phe Asn Ala Ser Thr Asp Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys
580 585 590

His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr
595 600 605

Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
610 615 620

Thr Val Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val
625 630 635 640

Glu His Arg Leu Thr Ala Ala Cys Asn Phe Thr Arg Gly Asp Arg Cys
645 650 655

Asn Leu Glu Asp Arg Asp Arg Ser Gln Leu Ser Pro Leu Leu His Ser
660 665 670

Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
675 680 685

Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
690 695 700

Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
705 710 715 720

Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
725 730 735

Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu

740 745 750

Glu Asn Leu Val Ile Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly
755 760 765

Leu Val Ser Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly
770 775 780

Arg Trp Val Pro Gly Ala Val Tyr Ala Leu Tyr Gly Met Trp Pro Leu
785 790 795 800

Leu Leu Leu Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr
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Glu Val Ala Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala
820 825 830

Leu Thr Leu Ser Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp Cys Met Trp
835 840 845

Trp Leu Gln Tyr Phe Leu Thr Arg Val Glu Ala Gln Leu His Val Trp
850 855 860

Val Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val Ile Leu Leu
865 870 875 880

Met Cys Val Val His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu
885 890 895

Leu Ala Ile Phe Gly Pro Leu Trp Ile Leu Gln Ala Ser Leu Leu Lys
900 905 910

Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu
915 920 925

Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala Ile Ile Lys
930 935 940

Leu Gly Ala Leu Thr Gly Thr Tyr Val Tyr Asn His Leu Thr Pro Leu
945 950 955 960

Arg Asp Trp Ala His Asn Gly Leu Arg Asp Leu Ala Val Ala Val Glu
965 970 975

Pro Val Val Phe Ser Arg Met Glu Thr Lys Leu Ile Thr Trp Gly Ala
980 985 990

Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala

995 1000 1005

Arg Arg Gly Gln Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val Ser
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Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr
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Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys
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Asn Gln Val Glu Gly Glu Val Gln Ile Val Ser Thr Ala Thr Gln Thr
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Phe Leu Ala Thr Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His Gly
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Ala Gly Thr Arg Thr Ile Ala Ser Pro Lys Gly Pro Val Ile Gln Met
1090 1095 1100

Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Pro Ala Pro Gln Gly
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Ser Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu
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Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser
1140 1145 1150

Arg Gly Ser Leu Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser
1155 1160 1165

Ser Gly Gly Pro Leu Leu Cys Pro Ala Gly His Ala Val Gly Leu Phe
1170 1175 1180

Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Ile
1185 1190 1195 1200

Pro Val Glu Asn Leu Gly Thr Thr Met Arg Ser Pro Val Phe Thr Asp
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Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu
1220 1225 1230

His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr
1235 1240 1245

Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala

1250 1255 1260

Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly Val Asp Pro
1265 1270 1275 1280

Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr
1285 1290 1295

Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly
1300 1305 1310

Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr
1315 1320 1325

Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly
1330 1335 1340

Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr
1345 1350 1355 1360

Val Ser His Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu
1365 1370 1375

Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly
1380 1385 1390

Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala
1395 1400 1405

Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly
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Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Val Val Val Ser
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Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp Ser Val Ile
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Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro
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Thr Phe Thr Ile Glu Thr Thr Thr Leu Pro Gln Asp Ala Val Ser Arg
1475 1480 1485

Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg
1490 1495 1500

Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val

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Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro
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Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu
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Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly
1555 1560 1565

Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly
1570 1575 1580

Glu Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg
1585 1590 1595 1600

Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile
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Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu
1620 1625 1630

Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr
1635 1640 1645

Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp
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Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser
1665 1670 1675 1680

Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro
1685 1690 1695

Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln Glu Phe Asp Glu Met
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Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu
1715 1720 1725

Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser
1730 1735 1740

Arg His Ala Glu Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys
1745 1750 1755 1760

Leu Glu Val Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile

1765 1770 1775

Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala
1780 1785 1790

Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly
1795 1800 1805

Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu
1810 1815 1820

Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly
1825 1830 1835 1840

Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu
1845 1850 1855

Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile
1860 1865 1870

Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro
1875 1880 1885

Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala
1890 1895 1900

Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met
1905 1910 1915 1920

Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr
1925 1930 1935

His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu
1940 1945 1950

Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile
1955 1960 1965

Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile
1970 1975 1980

Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys
1985 1990 1995 2000

Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln
2005 2010 2015

Arg Gly Tyr Arg Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg

2020 2025 2030

Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys Asn Gly Thr Met
2035 2040 2045

Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe
2050 2055 2060

Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro
2065 2070 2075 2080

Asn Tyr Lys Phe Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu
2085 2090 2095

Ile Arg Arg Val Gly Asp Phe His Tyr Val Ser Gly Met Thr Thr Asp
2100 2105 2110

Asn Leu Lys Cys Pro Cys Gln Ile Pro Ser Pro Glu Phe Phe Thr Glu
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Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro Cys Lys Pro Leu
2130 2135 2140

Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His Glu Tyr Pro Val
2145 2150 2155 2160

Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr
2165 2170 2175

Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg
2180 2185 2190

Arg Leu Ala Arg Gly Ser Pro Pro Ser Met Ala Ser Ser Ser Ala Ser
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Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Ala Asn His Asp
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Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu
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Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile
2245 2250 2255

Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Val
2260 2265 2270

Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg Phe Ala Arg Ala

2275 2280 2285

Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu Val Glu Thr
2290 2295 2300

Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu
2305 2310 2315 2320

Pro Pro Pro Arg Ser Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr
2325 2330 2335

Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala
2340 2345 2350

Thr Lys Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn
2355 2360 2365

Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys Pro Pro Asp Ser
2370 2375 2380

Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly
2385 2390 2395 2400

Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser Ser Gly Ala
2405 2410 2415

Asp Thr Glu Asp Val Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly
2420 2425 2430

Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn
2435 2440 2445

Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr Ser Thr
2450 2455 2460

Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val Thr Phe Asp Arg
2465 2470 2475 2480

Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu Lys Glu Val Lys
2485 2490 2495

Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala
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Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys Phe Gly Tyr Gly
2515 2520 2525

Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val Ala His Ile Asn

2530 2535 2540

Ser Val Trp Lys Asp Leu Leu Glu Asp Ser Val Thr Pro Ile Asp Thr
2545 2550 2555 2560

Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly
2565 2570 2575

Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg
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Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Lys Leu Pro Leu
2595 2600 2605

Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg
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Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly
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Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp
2645 2650 2655

Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln
2660 2665 2670

Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly
2675 2680 2685

Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg
2690 2695 2700

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2705 2710 2715 2720

Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu Gln Asp Cys Thr
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Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly
2740 2745 2750

Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr
2755 2760 2765

Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu
2770 2775 2780

Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly

2785 2790 2795 2800

Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu
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Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp
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Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile
2835 2840 2845

Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu
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Gln Ala Leu Asn Cys Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro
2865 2870 2875 2880

Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe
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Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys
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Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala
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Arg Ser Val Arg Ala Arg Leu Leu Ser Arg Gly Gly Arg Ala Ala Ile
2930 2935 2940

Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu
2945 2950 2955 2960

Thr Pro Ile Ala Ala Ala Gly Arg Leu Asp Leu Ser Gly Trp Phe Thr
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Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val Ser His Ala Arg
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